ESSENTIALS OF PHYSIOLOGY

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WITH 134 ILLUSTRATIONS

LONGMANS, GREEN, AND CO.
39 PATERNOSTER ROW, LONDON
FOURTH AVENUE & 30TH STREET, NEW YORK
BOMBAY, CALCUTTA, AND MADRAS
1914

PREFACE

Our object in writing this book has been to bring together in a concise form the fundamental facts and principles of Physiology, primarily with the object of meeting the requirements of the medical student preparing for a pass examination in the subject of Physiology. Considerations of space have led us to exclude as far as possible histological details and descriptions of chemical and experimental methods which form part of each student's laboratory course, and for which separate text-books are used. We have also omitted, for the same reason, all matter of purely historical interest.

In view of the transitional state of anatomical nomenclature, we have, after much consideration, retained the terminology hitherto used in this country, and have inserted the Basle nomenclature in brackets.

While it is impossible to mention all the sources upon which we have drawn, we wish to acknowledge our especial indebtedness to Professor Starling, not only for permission to use many figures from his *Principles of Physiology*, but also for advice and information on many points. Our thanks for permission to use figures, which are as far as possible separately acknowledged in the text, are also due to Professor Sir E. A. Schäfer (*Quain's Anatomy* and *Essentials of Histology*), Professor J. N. Langley (*Journal of Physiology*), Dr M. S. Pembrey (*Practical Physiology*), J. Barcroft, Esq. (*Respiratory Function of the Blood*), Dr A. Hertz, Dr Homans, Dr W. E. Hume, Professor R. Howden (*Gray's Anatomy*), and the Council of the Royal Society. We must also thank the Publishers and others who have kindly supplied us with blocks, namely, Messrs J. & A. Churchill, Hodder & Stoughton, Macmillan & Co., Ltd., Mr Edwin Arnold, the Cambridge University Press, Messrs Baird & Tatlock, Ltd., and Messrs Hawksley.

Finally, we are indebted to Miss F. H. Miller for her unwearying efforts in the production of the original illustrations, and to Messrs Longmans, Green & Co. for the great pains they have taken in the reproduction of the figures.

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ESSENTIALS OF PHYSIOLOGY.

CHAPTER I.

INTRODUCTORY.

Every living structure is derived, so far as our present knowledge goes, from another living structure and exhibits certain well-marked features. It takes up non-living material and builds it up in a more or less modified form into its own framework, it has the power of growing up to a certain limit, and it is capable of giving rise to other living organisms like itself. Further, it has the property of irritability, that is, it may be affected by a change in its immediate surroundings which is called a stimulus, and to which it responds by some change in itself, usually movement or secretion. These manifestations of life form the subject-matter of the science of Physiology, which naturally falls into two divisions, Vegetable and Animal. With the former of these, however, we are not here concerned.

The functions of animal life may be studied in their most primitive condition in a unicellular organism, such as amœba. This minute creature may be observed under the microscope to enfold particles of food material, to assimilate what is useful in these particles, and to reject what is useless; it may be seen to respond to chemical or mechanical stimuli by movement, sometimes contracting into the smallest bulk by becoming spherical, at other times protruding part of its substance and transferring itself, as it were, into the protruded part, and so changing its position. It may also be observed at a certain stage in its life to divide into two, and each of the young amœbæ so produced grows until it too gives rise in its turn to another generation.

In the higher animals the body is composed of a multitude of cells, and this complexity of structure is accompanied, as in a community of persons, by a specialisation of function whereby certain cells are

modified to subserve movement, others to produce secretions, and so on; in this way the efficiency of the organism as a whole is increased. Obviously in such a community of cells it is of the utmost importance that the various groups should work in harmony, and to ensure this they must be linked up by some controlling mechanism.

Two such mechanisms are found in the body: (1) a system of chemical messengers, or *hormones*, and (2) the *nervous system.* The former is the more primitive of the two methods. A hormone is produced in one organ and is carried by the blood to another, exciting or restraining its activity. For example, as the acid contents of the stomach pass into the bowel they lead to the production of a hormone in the intestinal wall. The newly formed substance is taken up by the blood and carried to the pancreas, which it stimulates to secrete the juice required for the next stage of the digestive process. Such a method of communication is comparatively slow, and where rapidity of transmission is important the messages are conveyed by the nervous system. The latter, in fact, bears much the same relation to the blood current as the telegraphic system bears to ordinary letter post. Thus if a foreign body touches the surface of the eyeball, information of the fact is sent along certain nerve fibres to the brain, and impulses return to the muscles of the eyelids, causing the lids to close, within a small fraction of a second.

In any living organism the unit of structure is a minute, jelly-like mass known as a *cell.* The simplest organisms consist of a single cell, those which are higher in the scale of life being composed of many cells. Each cell is composed of a semi-fluid material, known as protoplasm, containing a denser circumscribed structure, the nucleus. In some cases a well-defined cell-envelope exists, notably in vegetable cells and in the mammalian ovum, but in many animal cells no definite envelope can be demonstrated, and in these the boundary is probably determined by the condensation of molecules which is known to take place on the surface of colloid solutions, and which gives rise to the physical condition known as surface tension.

Protoplasm is semi-transparent, and may be homogeneous in appearance, or may show traces of structure in the form of a network containing hyaline fluid in its meshes. It is the working part of the cell, and often contains granules which represent the products of its activity. Such granules are especially seen in secreting cells, and occupy corresponding spaces in the cell protoplasm. Protoplasm itself varies greatly in composition, but it always contains a large proportion of albuminous substances or proteins.

The *nucleus* is essential to the life of the cell. When a cell is

divided into a part which contains the nucleus and a part which does not, an experiment which may be performed with the larger unicellular organisms, the part separated from the nucleus becomes inactive and dies. Further, when cell-division occurs, the nuclear changes which lead to the formation of two daughter nuclei precede the division of the protoplasm. The nucleus also differs in chemical composition and in staining reactions from the rest of the cell. It contains a substance called nuclein, which is a compound of nucleic acid with protein. Nucleic acid is distinguished by containing a considerable proportion of phosphorus in its molecule.

In the human body all the tissues and organs subserve, directly or indirectly, the production of movement, whether that takes the form of locomotion, work, speech, or writing. The nervous and muscular tissues are the master tissues of the body, the remaining tissues and organs being designed for their protection and nutrition. The bony skeleton forms a framework which is necessary for the carrying out of movements, and which shields the brain and other important structures from injury. The skin is also protective in function, and, with the eye, ear, and other sense organs, it receives impressions from the outer world which are of service in determining the bodily activities. The digestive tract converts insoluble food substances into soluble bodies which are then absorbed into the blood. The circulatory system conveys the blood to all the cells and tissues of the body so that they receive nourishment. The blood also receives from the cells and tissues the waste products formed by their activity and carries these to the lungs and kidneys, by which they are excreted. Besides excreting one of the waste products, carbonic acid, the lungs take up oxygen from the air and convey it to the blood, from which it passes to the cells and tissues. Further, in addition to the glands which secrete the digestive and other juices, there are in the body certain glands whose function it is to produce various hormones. All these subsidiary systems are only of importance in that they serve to sustain the muscular and nervous structures. The muscular system, in its turn, is to be looked upon as the organ of expression of the nerve centres. The life of the body, therefore, consists ultimately in its nervous activities.

CHAPTER II.

THE CHEMISTRY OF THE BODY.

The body of an animal is composed of water, organic compounds, and inorganic salts. If the body, or any part of it, be dried at a temperature of 105° C., the loss of weight indicates the amount of water present. If the dried solids be exposed to a high temperature in the presence of oxygen, the organic compounds are all oxidised, and the residue consists of the inorganic matter.

THE INORGANIC SALTS.

The chief salts which are found in the body are the chlorides, phosphates, sulphates, and carbonates of sodium, potassium, calcium, and magnesium. Iodine, fluorine, and a few other chemical elements are also present in small amount; iron enters into the composition of the coloured corpuscles of the blood. Generally speaking, sodium is the base most largely present in the body fluids, such as the plasma of the blood, and potassium is that most abundant in the cells and tissues; while the bones owe their rigidity to the large proportion of calcium phosphate and carbonate which they contain.

The functions of the inorganic salts are various, and are not yet completely understood. The waste carbonic acid from the tissues is conveyed to the lungs partly in the form of carbonates and bicarbonates. Sulphates and phosphates are to some extent waste products derived from the breaking down of organic compounds. Phosphates also serve a useful purpose in maintaining the balance between acids and bases in the body by undergoing change from mono- to di-hydrogen phosphate, or the reverse, as occasion requires. The salts as a whole, but especially the chlorides, have, moreover, important functions depending upon their physical properties (p. 14).

THE ORGANIC COMPOUNDS.

The organic constituents of the body fall naturally into two main groups, non-nitrogenous and nitrogenous. The substances comprised in these two groups may be looked upon as fragments of the protoplasm

or living material of the cell, for analysis necessarily involves the death of the living structure. It is clear, however, that protoplasm itself is largely composed of nitrogenous material, though it derives much of the energy necessary for its activities from the combustion of the non-nitrogenous compounds.

THE NON-NITROGENOUS SUBSTANCES.

These again fall into two groups: (1) those in which the combined oxygen is sufficient to oxidise all the hydrogen of the molecule, and (2) those in which the oxygen is insufficient to combine with the hydrogen of the molecule.

(I.) The former group consists of the **Carbohydrates**, and the members of it which occur normally in the body are either hexoses, that is, each contains six carbon atoms in its molecule, or are formed by a combination of two or more hexose molecules. Pentoses, with five carbon atoms each, also occur; an example is xylose, which enters into the formation of the molecule of the nucleic acid derived from the pancreas. The carbohydrates found in the body are dextrose, lævulose (fructose), galactose, lactose, and glycogen. Others occur as constituents of food, *e.g.* cane-sugar and starch. The first three have the formula $C_6H_{12}O_6$, and belong to the group of mono-saccharides. Lactose is a disaccharide, that is, it belongs to a group of substances formed by the condensation of two monosaccharide molecules with the abstraction of a molecule of water.

$$2C_6H_{12}O_6 - H_2O = C_{12}H_{22}O_{11}.$$

Glycogen is a polysaccharide, and is formed by the condensation of a large number of monosaccharide molecules, as in the formula

$$nC_6H_{12}O_6 - nH_2O = (C_6H_{10}O_5)_n.$$

The symbol "n" may have a very high value. Thus starch is supposed to have the formula $200(C_6H_{10}O_5)$.

The Monosaccharides.—Dextrose may be looked upon as the current carbohydrate coin of the body. It is a soluble crystalline substance, having the formula

$$\begin{array}{c} CH_2OH \\ | \\ (CHOH)_4. \\ | \\ CHO \end{array}$$

It is an aldehyde, and, like other aldehydes, when heated with an alkaline solution of a cupric salt, it reduces the latter with the formation of yellow cuprous oxide. This property of dextrose and other "reducing sugars" forms the basis of the tests of Trommer, Fehling,

and Benedict. Dextrose has also the power of reducing acid solutions of cupric salts, differing in this respect from reducing sugars which belong to the class of disaccharides. On being heated with phenylhydrazine and acetic acid, dextrose forms a compound, phenylglucosazone, which crystallises in yellow needles, generally arranged in loose sheaves. Solutions of dextrose are decomposed by the action of yeast into carbonic acid and alcohol. Further, dextrose is dextro-rotatory, that is, its solutions rotate the plane of polarised light to the right.

Lævulose (fructose) and galactose occur in the body in smaller quantity. The former is lævo-, the latter dexto-rotatory. Like dextrose, they have the property of reducing alkaline solutions of cupric salts, and they also form osazones.

Dextrose and galactose are aldehydes and are known as aldoses, while lævulose is a ketone and belongs to the group of ketoses.

CHO	CH_2OH	CHO
H.C.OH	CO	H.C.OH
HO.C.H	HO.C.H	HO.C.H
H.C.OH	H.C.OH	HO.C.H
H.C.OH	H.C.OH	H.C.OH
CH_2OH	CH_2OH	CH_2OH
Dextrose	Lævulose	Galactose

The only *disaccharide* which occurs in the body is lactose, the sugar of milk. Two other disaccharides, cane sugar and maltose, are of physiological importance, the former being an important food-stuff, the latter an intermediate stage in the digestion of starch. Lactose and maltose are reducing sugars and form characteristic osazones. Each of the three, when boiled with dilute mineral acid, undergoes hydrolysis, the molecule taking up water and being split into two molecules of a monosaccharide.

$$C_{12}H_{22}O_{11} + H_2O = 2C_6H_{12}O_6.$$

The *polysaccharide*, glycogen or animal starch, occurs chiefly in the liver and muscles as a storage product. Its solution in water differs from that of vegetable starch, which is also a polysaccharide (1) in that it is more markedly opalescent than that of the latter, and (2) in giving a reddish brown colour with iodine, whereas vegetable starch gives a blue colour. The polysaccharides do not reduce alkaline solutions of cupric salts. They undergo hydrolysis when boiled with dilute mineral acid or as the result of ferment action, yielding first poly-

saccharides of smaller molecule than the starches, called dextrins, and a disaccharide, maltose, and giving as the final product the monosaccharide, dextrose.

The first-formed dextrin products of the hydrolysis of the starches are called erythro-dextrins, because they give a red colour with iodine; the later-formed substances are called achroo-dextrins because they give no colour with iodine, and consist of smaller molecules than the erythro-dextrins. The process of hydrolysis of a polysaccharide may be summarised in the equation

$$(C_6H_{10}O_5)_n + nH_2O = nC_6H_{12}O_6.$$

Inosite.—Inosite is a substance found in muscle and formerly called muscle-sugar. It has the formula $C_6H_{12}O_6 + 2H_2O$, but does not belong to the carbohydrate group, being a benzene derivative. It does not reduce an alkaline solution of cupric sulphate, does not rotate polarised light, and is non-fermentable.

(II.) The second group of non-nitrogenous substances, those in which the oxygen of the molecule is insufficient to combine with the hydrogen, consists of the **Fats**. The chief fats found in the body are tristearin, $C_3H_5(C_{18}H_{35}O_2)_3$, tripalmitin, $C_3H_5(C_{16}H_{31}O_2)_3$, and triolein, $C_3H_5\ (C_{18}H_{33}O_2)_3$. They are compounds of the corresponding fatty acids, stearic, palmitic, and oleic, with the trivalent alcohol, glycerol. Stearic and palmitic acids are saturated compounds, and the former and its esters, being higher in the series than palmitic acid and its esters, have a higher melting point. Oleic acid is unsaturated, and both the acid itself and triolein have a relatively low melting point, being fluid at room temperature.

Fats are insoluble in water, but are soluble in ether or in warm alcohol. They are decomposed on heating with alkalies, the fatty acid uniting with the alkaline base to form a soap and the glycerol being set free (saponification). If a neutral fat, such as pure olive oil, is shaken up with water, the fat becomes broken up into fine globules which run together again when the shaking ceases. If, however, some soap is present, each globule becomes coated with a layer of soap molecules, which so reduce the surface tension between the fat and the water that the globules remain apart. Such a suspension of fat globules is called an emulsion. A fine emulsion of this kind occurs in the lymph during the absorption of fat, the place of the soap being probably taken by the proteins of the lymph itself.

Lipoids.—The term lipoids includes a number of substances which resemble fats in being soluble in ether. The commonest of these are lecithin and cholesterol, which are constantly associated in the body,

occurring especially in the nervous tissues, bile, and the plasma and corpuscles of the blood.

Lecithin is a complex fat, and when boiled with baryta water yields two fatty acids, glycerophosphoric acid, and choline, which belongs to the group of amines. Lecithin, in virtue of its nitrogen content, has also affinities with proteins. It belongs to the group of phospholipines, which also includes cephaline and sphingo-myeline. Some other lipoid substances found in the brain resemble lecithin in containing nitrogen, but contain no phosphorus.

Cholesterol, $C_{27}H_{45}OH$, is a complex monatomic alcohol, and is included in the group of lipoids simply on account of its solubilities. It forms colourless, square, flat crystals, often notched at one corner, and gives a red colour with strong sulphuric acid.

Lipoid substances enter into the composition of cell protoplasm, occurring especially in the superficial layer, or "plasma skin." This surface layer is less permeable to salts and other substances in watery solution than to water. Substances such as alcohol and alkaloids, which are soluble in oily media, can penetrate the cell.

THE NITROGENOUS SUBSTANCES.

The nitrogenous substances contained in the body are (1) proteins, which form the greater proportion of the solid constituents of the cells, tissues, and body fluids, and (2) derivatives of proteins.

The Proteins.

The physical properties of proteins are those of colloid substances (p. 16). Some proteins, however, may be obtained in the crystalline form, for example egg-albumin, and hæmoglobin, the pigment of blood. Others, for example peptone (which is not, however, a constituent of the body), are capable of diffusing through an animal membrane.

The molecule of protein is very large; it contains the elements C, H, N, O, and S in the following proportions:—

C	50·6 – 54·5	per cent.
H	6·5 – 7·3	,,
N	15·0 – 17·6	,,
O	21·5 – 23·5	,,
S	0·3 – 2·2	,,

Proteins have the power of combining either with acids or alkalies, and this property is of service in maintaining the reaction of the cells and fluids of the body at its normal level.

When a solution of a protein, such as egg-albumin, is warmed with dilute acid or alkali, it is converted into *metaprotein* and shows

changes in its characters. The egg-albumin solution is neutral, and is coagulated on heating if salts are present. The metaprotein solution does not coagulate on heating, and gives a precipitate of metaprotein on neutralisation, the precipitate being soluble in excess of either acid or alkali.

If a solution of egg-albumin is subjected to the action of superheated steam, or is boiled for a long time with mineral acid, or is subjected to the action of gastric juice or of pancreatic juice, the albumin takes up water and the molecule is finally split up into small molecules, the process being known as hydrolysis. The splitting up occurs in stages, the molecules becoming progressively smaller. After the substance has passed through a metaprotein stage, a series of *hydrated proteins* are formed, the first formed products being called *proteoses* and the later ones *peptones*. The hydrated proteins are soluble in water and are not coagulated on boiling. Proteoses are distinguished from peptones in that they are precipitated if their solution is saturated with ammonium sulphate, whereas peptones are not precipitated in this way. If the hydrolysis is continued, the peptones are further split into substances called *polypeptides*, which do not show protein characteristics, and which consist of groupings of *amino-acids*. By still further hydrolysis these are split into their constituent amino-acids.

All proteins give certain colour reactions by which their presence in solutions may be recognised. The most useful of these are the following :—

(1) *The Xanthoproteic reaction.*—Nitric acid is added to the solution and it is boiled. A yellow colour is produced, which changes to orange on cooling and adding ammonia.

(2) *Millon's reaction.*—A solution of mercuric and mercurous nitrates is added to the protein solution. A precipitate is formed and becomes red on heating.

(3) *Piotrowski's reaction.*—With dilute copper sulphate and excess of caustic alkali, most proteins give a violet colour, but in the case of proteose or peptone the colour is pink.

(4) *Hopkins' reaction.*—Glyoxylic acid is added to the protein solution, and then strong sulphuric acid is poured down the side of the tube so as to form a layer at the bottom. A violet colour is produced at the junction of the two fluids.

Millon's reaction depends upon the presence of tyrosine in the protein molecule; Hopkins' reaction depends upon the presence of tryptophane. Gelatin, which does not contain either tyrosine or tryptophane, gives neither of these reactions.

The chief proteins found in the body are (1) protamines, (2) histones,

(3) albumins, (4) globulins, (5) phosphoproteins, (6) scleroproteins, and (7) conjugated proteins.

(1) *Protamines* are basic in character and only occur in combination. They are chiefly found, combined with nucleic acid, in the spermatozoa of certain fishes.

(2) *Histones* are also basic in character, and occur in the combined form. An example is globin, the protein constituent of hæmoglobin.

(3 and 4) *Albumin* and *globulin* occur in all cells and in many of the body fluids, and are distinguished from each other by their solubilities. Albumin is soluble in water or weak salt solution, and its molecules are aggregated to form a precipitate in a saturated solution of ammonium sulphate. Globulin is insoluble in water, soluble in weak salt solution, and is precipitated in a half-saturated solution of ammonium sulphate. Albumin or globulin in solution, on being heated, undergoes first of all a change which is probably chemical in nature, and is known as denaturation. A physical change follows, and consists in the aggregation of the molecules to form a coagulum. The presence of inorganic salts is favourable to aggregation, but is unfavourable to denaturation. Acids and alkalies, on the other hand, favour denaturation but hinder aggregation. Thus, if the protein is heated with more than the merest trace of acid or alkali, an acid or alkaline solution of metaprotein is obtained which will not coagulate on heating, but yields a precipitate of metaprotein on neutralisation. A trace of acid favours coagulation of an albumin or globulin solution, because the acid combines with the protein to form a salt.

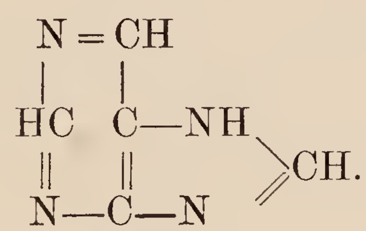
The effect of salts in favouring the coagulation or precipitation of proteins is due to the ionisation of the salt. A solution of protein is really a suspension, and the suspended particles carry an electric charge, which is positive in an acid solution, negative in an alkaline solution. As all the particles carry a similar charge, they will tend to repel one another, but if the charge be reduced, precipitation or coagulation will take place. Hence, in the case of an ionised salt, the effective ion which brings about coagulation is that which carries a charge opposite in sign to that of the protein particles. It is found that the effectiveness of an ion is determined by its valency. In the case of acid solutions the trivalent anion of potassium citrate has a greater coagulating power than the divalent SO_4, and the latter again is more effective than the monovalent Cl. So also in alkaline solutions, barium chloride with a divalent kation is more effective than sodium chloride with a monovalent Na ion.

(5) *Caseinogen*, the chief protein of milk, is a phosphoprotein, that

is, it contains phosphorus combined in its molecule in addition to the five elements common to proteins generally. It is insoluble in water, but soluble in weak alkalies, and is precipitated from its alkaline solution by acetic acid, the precipitate being soluble in excess of the acid. The alkaline solution is not coagulated by heat.

(6) The *Scleroproteins* are distinguished by their relative insolubility. They form the chief constituents of the fibrous and horny structures of the body. Thus, white fibres are mainly composed of collagen, yellow fibres of elastin, and hair, horn, and hoofs of keratin. When collagen is boiled with water it yields gelatin, a substance which is soluble in boiling water, the solution setting to a jelly on cooling. Elastin and keratin are both insoluble in hot or cold water, dilute acids or alkalies, or in alcohol or ether. Keratin is remarkable for the amount of sulphur contained in its molecule.

(7) *The Conjugated Proteins.*—These are nucleoprotein, glucoprotein, and chromoprotein, and each consists of a protein combined with another body called the prosthetic group. *Nucleoproteins* are a constant constituent of cell nuclei. They are soluble in water, weak salt solution, or dilute alkalies. They possess acid characters, hence the affinity of nuclear chromatin, which contains nucleoprotein, for basic dyes. A nucleoprotein is a compound of a protein with nuclein, and the latter consists of protein combined with nucleic acid, an organic acid containing phosphorus. If a nucleoprotein is subjected to digestion by gastric juice, an insoluble brownish residue is obtained. This residue consists of nuclein. If the nucleic acid obtained from nuclein is hydrolysed, the two substances, adenine and guanine, are constantly found among the products of disintegration. These two bodies belong to the purin group, that is, they may be regarded as derivatives of purin, which has the formula



Adenine has the formula $C_5H_5N_5$, while *guanine* is $C_5H_5N_5O$. Both these substances, when oxidised, yield uric acid, $C_5H_4N_4O_3$.

In *glucoprotein* the combined body is a carbohydrate radical, often glucosamine ($C_6H_{13}NO_5$), and therefore containing nitrogen; the glucosamine is split off when the glucoprotein is boiled with mineral acid. It reduces alkaline solutions of cupric salts. Most glucoproteins belong to the group of *mucins*. These are soluble in weak alkalies, they are not coagulated by heat, and they are precipitated by acetic

acid, the precipitate being insoluble in excess of the acid. The mucoids, for example ovomucoid, are also glucoproteins.

The best example of a *chromoprotein* is the blood pigment, hæmoglobin, in which a protein, globin, is combined with an iron-containing body, hæmatin. Hæmoglobin crystallises with comparative ease, and is freely soluble in water.

The Derivatives of Proteins.

When a protein molecule is broken up, either by prolonged boiling with a mineral acid, or by the action of certain enzymes, the resulting products are found to belong to the class of *amino-acids*; that is, they are fatty acids in which one or more atoms of hydrogen have been replaced by NH_2 groups. Some of these acids are combined with the benzene ring, *e.g.* tyrosine and tryptophane; two, proline and oxyproline, contain the pyrrol ring; one, histidine, the iminazol ring; and one, cystine, contains sulphur, that is, it is a thioamino-acid. Whereas the fats of the body belong to the upper end of the fatty acid series, it is to be noted that the amino-acids belong to the lower end of the same series. The simplest amino-acid found in the body is glycine, or amino-acetic acid, $CH_2.NH_2.COOH$. This is one of the most abundant derivatives of gelatin. The next in the series, alanine or amino-propionic acid, occurs in abundance, both in its simple form, $CH_3.CH.NH_2.COOH$, and also combined, with phenyl as phenylalanine, with oxyphenyl as tyrosine ($C_6H_4.OH.CH_2CH.NH_2COOH$), with indol as tryptophane, with iminazol as histidine, and with sulphur as cystine. Although analysis of any one protein will yield all or most of the amino-acids which have so far been isolated, nevertheless the relative proportions of amino-acids contained in different proteins vary widely, and to this variation the proteins probably owe their distinctive characteristics. Gelatin is remarkable in containing no tyrosine, tryptophane, or cystine.

The following tables from Starling's *Principles of Human Physiology* give (1) a list of amino-acids, and (2) the proportion of the different amino-acids contained in various proteins.

Mono-amino-acids.

Glycine (amino-acetic acid)	Monobasic acids of fatty series.
Alanine (amino-propionic acid)	
Serine or oxyalanine (oxyamino-propionic acid)	
Amino-valerianic acid	
Leucine (amino-isobutylacetic acid)	
Isoleucine (amino-caproic acid)	
Aspartic acid	Dibasic acids.
Glutamic acid	

Phenylalanine . . . . . Tyrosine (oxyphenylalanine) . . .	Benzene derivatives.
Proline (pyrrolidine carboxylic acid) . Oxyproline (oxypyrrolidine carboxylic acid) . . . . . . Tryptophane (indolamino-propionic acid)	Heterocyclic compounds.

Diamino-acids and their Compounds.

Lysine (diamino-caproic acid) . . Arginine (guanidinamino-valerianic acid) Histidine (iminazolalanine) . . .	The "hexone bases."

Diamino-tryoxydodecoic acid (derived from a 12-carbon acid).
Cystine (derived from amino-thiopropionic acid).

Arginine is not a simple amino-acid, but is a compound of amino-valerianic acid with guanidine. A similar compound of guanidine occurs in muscle as *creatine*, or methylguanidine acetic acid. When creatine is boiled with baryta water it is split into urea and sarcosine (methyl-glycine), thus giving rise to an amino-acid.

	Serum Albumin.	Egg Albumin.	Edestin (hemp seeds).	Gliadin.	Caseinogen.	Globin.	Salmin.	Sturin.	Gelatin.	Keratin (from horse-hair).
Glycine . .	0·0	0·0	3·8	0·9	0·0	0·0	0·0	...	16·5	4·7
Alanine . .	2·7	8·1	3·6	2·7	1·5	4·2	...	...	0·8	1·5
Serine . .	0·6	...	0·33	0·12	0·5	0·6	7·8	...	0·4	0·6
Amino-valerianic acid . .	...	...	present	0·3	7·2	...	4·3	...	1·0	0·9
Leucine . .	20·0	7·1	20·9	6·0	9·35	29·0	0·0	...	2·1	7·1
Proline . .	1·0	2·25	1·7	2·4	6·70	2·3	11·0	...	5·2	3·4
Oxyproline .	...	...	2·0	...	0·23	1·0	...	...	3·0	...
Glutamic acid .	7·7	8·0	6·3	36·5	15·55	1·7	...	...	0·88	3·7
Aspartic acid .	3·1	1·5	4·5	1·3	1·39	4·4	...	...	0·56	0·3
Phenylalanine .	3·1	4·4	2·4	2·6	3·2	4·2	...	...	0·4	0·0
Tyrosine . .	2·1	1·1	2·1	2·4	4·5	1·5	...	...	0·0	3·2
Tryptophane .	present	present	present	1·0	1·50	present	...	...	0·0	...
Cystine . .	2·3	0·2	0·25	0·45	?	0·3	...	...	...	over 10
Lysine . .	...	2·15	1·0	0·0	5·95	4·3	0·0	12·0	2·75	1·1
Arginine . .	...	2·14	11·7	3·4	3·81	5·4	87·4	58·2	7·62	4·5
Histidine . .	...	...	1·1	1·7	2·5	11·0	0·0	12·9	0·4	0·6

The second of these tables shows that the special characteristics of the separate proteins are associated with differences in the relative proportions of their constituent amino-acids, and it has also been shown that there are differences in the way in which the amino-acids are

grouped to form the protein molecule. Moreover, when a protein is hydrolysed by boiling with a mineral acid, the proportion of nitrogen which is recovered in the form of ammonia, of monoamino-, and of diamino-nitrogen varies considerably according to the protein examined. It is especially noticeable that, whereas monoamino-acids are most abundant in albumin and globulin, protamines, for example salmine, derived from the spermatozoa of the salmon, are especially rich in basic (diamino) nitrogen.

PHYSICAL PROCESSES WHICH OCCUR IN THE BODY.

Ions.—When sodium chloride is dissolved in water its molecules undergo dissociation into sodium *ions*, which are charged with positive electricity, and chlorine ions, which are charged with negative electricity. Ions are not necessarily the same as atoms, since a solution of sulphuric acid in water contains hydrogen ions and SO_4 ions. Substances which undergo dissociation when in solution are called *electrolytes*, since an electrical current passed through such a solution is conducted by the movement of the ions; and owing to the presence of electrolytes in the tissues of the body, these are able to conduct electrical currents. Many substances, however, such as sugar, when dissolved in water do not undergo dissociation, and the dissolved molecules carry no electrical charge.

Diffusion and Osmosis.—When a substance such as sodium chloride is dissolved in water, the dissolved molecules behave like the molecules of a gas; they are in constant movement and exert pressure upon the walls of the vessel containing them. If, for example, a vessel is divided into two compartments by a vertical membrane, and if one compartment is filled with water and the other with 1 per cent. salt solution, the molecules of salt in their movements will beat upon the membrane; and if the latter is *permeable* to molecules of salt, they will pass through it into the distilled water until the amount of sodium chloride on the two sides of the membrane becomes equal. This process is known as diffusion, and the rate at which it occurs varies with the percentage of sodium chloride originally present in the solution.

If the membrane allows water but not sodium chloride to pass through it, it is said to be *semi-permeable*, and the pressure exerted by the molecules of salt upon the membrane is called *osmotic pressure* and can be measured in the following manner. A semi-permeable membrane is made by filling the pores of an earthenware cell with silicic acid or copper ferrocyanide; the cell is filled with 1 per cent. sodium

chloride solution, closed by a cork through which passes a tube attached to a mercurial manometer, and immersed in distilled water (fig. 1). Since the molecules of salt cannot pass through the membrane, they exert pressure on the wall of the cell and the surface of the mercury; water passes through the membrane into the cell, and the mercury is forced downwards in one limb of the manometer and upwards in the other until the difference of height in the two limbs is 5000 mm. Hg. This pressure balances the osmotic pressure exerted by the molecules of salt; and in raising the column of mercury the salt solution does work. If a 2 per cent. salt solution is used, the osmotic pressure is twice as great.

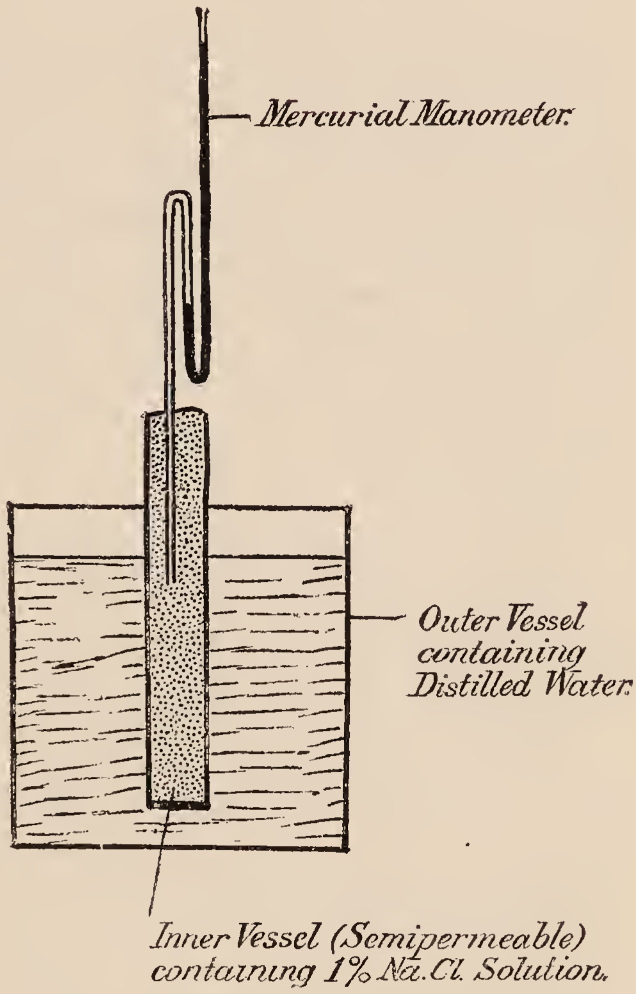


Fig. 1.—Osmometer. (Starling's *Elements of Physiology.*)

Similar experiments with other substances show that the osmotic pressure of any substance in solution depends, not upon its nature, but solely on the number of its molecules in solution, and is proportional therefore to the concentration of the solution. A gram-molecule of any substance is its molecular weight in grams. The molecular weight of dextrose is 180, and a gram-molecule of dextrose is 180 grams. A gram-molecular solution of dextrose contains 180 grams in 1 litre, whereas a similar solution of sodium chloride contains 58·5 grams per litre. If the sodium chloride did not dissociate, the two solutions would contain the same number of molecules and their osmotic pressure would be the same. But since sodium chloride does dissociate and each of its ions behaves like a molecule as regards osmotic pressure, the solution of sodium chloride, if completely dissociated, will exert twice the osmotic pressure of the solution of dextrose.

It is difficult to measure osmotic pressure in the manner just described, since the membranes are apt to give way and leak; and indirect methods are usually employed, of which the best is the determination of the freezing-point of a solution. When a substance is dissolved in water, the freezing-point of the water is lowered, the lowering being proportional to the concentration and osmotic pressure

of the dissolved substance. The lowering of the freezing-point below 0° C. is expressed by the letter Δ.

When a gram-molecule of any substance is dissolved in 1 litre of water the freezing-point is lowered by 1·87° C., and its osmotic pressure = 17,000 mm. Hg. The osmotic pressure of a substance in solution can be calculated from the formula

$$\text{Osmotic pressure} = \frac{\Delta}{1{\cdot}87^\circ \text{ C.}} \times 17{,}000 \text{ mm. Hg.}$$

Solutions which have the same osmotic pressure are said to be *isotonic*, and the tissues in mammals are isotonic with a solution containing 0·9 per cent. sodium chloride in water; this is known as normal saline solution. When the tissues are immersed in stronger, *i.e. hypertonic*, salt solution, water passes from the tissue into the salt solution by osmosis; when the salt solution has a lower osmotic pressure than the tissues, it is *hypotonic*, and the tissues take up water from the solution. In an isotonic solution, the tissues neither take up nor lose water.

Both osmosis and diffusion take place in the body, but the membranes are not completely impermeable to substances such as sugar or salt, so that osmosis is soon brought to an end by the passage of these substances through the membrane.

Colloids.—The term colloid was originally applied to all substances, such as starch and proteins, which would not form crystals or pass through an animal membrane, in contra-distinction to easily crystallisable bodies, such as sugar, which diffuse rapidly through animal membranes and are called crystalloids.

It is now known that the colloidal form is a state in which substances exhibit certain characteristic features, and that a very large number of substances, including metals, may exist in the colloidal form. Further, some colloids, such as hæmoglobin, are crystallisable.

Most colloids consist of very large molecules or aggregates of molecules, and their characters depend largely on the fact that they do not form true solutions in water or other solvents, but that their pseudo-solutions consist of particles, suspended in a very dilute solution of the colloid. Owing to the size of the particles, colloidal suspensions do not follow the laws of true solution, and they exert only a very small osmotic pressure.

If an electrolyte, such as sodium chloride, is added to a colloidal suspension, the salt concentrates at the surface of each colloidal particle, this being called *adsorption*. Its occurrence can be readily demonstrated by dipping strips of blotting paper, which is colloidal,

into a solution of a dye. The dye accumulates on the particles in the paper, and the latter becomes more deeply coloured than the solution into which it is dipped.

The amount of adsorption is relatively much greater in dilute than in strong solutions of the electrolyte. Its importance lies in the fact that the velocity with which a chemical change takes place varies with the concentration of the interacting substances. If two electrolytes, which can interact, are added to a colloidal solution, they become concentrated on the surface of the colloidal particles, and at these surfaces the reaction between them will proceed more rapidly than if the colloid were absent.

Solutions of colloids are called sols; in certain circumstances the particles may aggregate into larger masses, forming a precipitate, or the solution may change to a jelly, called a gel. An example of this process is the coagulation of protein by heat.

CHAPTER III.

MUSCLE.

Three varieties of muscular fibres are found in the body, namely, those forming skeletal muscle, those found in the walls of the blood-vessels, digestive tract, uterus, and other organs, and those in cardiac muscle. The structure of cardiac muscle will be considered later (page 177). The skeletal muscles, which are under the control of the will, are called voluntary muscles, the other kinds of muscle being termed involuntary, since, although they are under the control of the central nervous system, they are independent of the will.

VOLUNTARY MUSCLE.

A skeletal muscle consists of fibres bound together by connective tissue. The fibres have an average diameter of 50μ and vary in length, some being as long as 3 to 4 cm. Each fibre is enclosed in a delicate elastic sheath (sarcolemma), and shows alternating light and dark bands crossing it transversely; owing to the presence of these stripes, this form of muscle is often called striped or striated muscle. Each fibre contains a number of oval nuclei; in mammals these lie immediately under the sarcolemma, but in frogs they are scattered throughout the substance of the fibre. In a stretched fibre a narrow clear line, known as Hensen's line, can sometimes be seen running transversely in the middle of each dark band. Frequently, too, a dotted line is visible in the middle of each light band; it is termed Krause's membrane.

The fibres consist of fibrils, or *sarcostyles*, which run longitudinally and are imbedded in a material known as *sarcoplasm*. It is probable that each sarcostyle is made up of a number of short segments called *sarcomeres*, but the exact structure of the sarcostyles and the significance of Krause's membrane and Hensen's line in different animals is still uncertain. Schäfer has shown that the sarcostyles in the rapidly contracting wing muscles of insects are divided by the membranes of Krause into sarcomeres. He considers that the dark central part (or

sarcous element) of each sarcomere is divided into two parts by Hensen's line, and pervaded with longitudinal canals which are open towards Krause's membrane; and when the muscle contracts, the clear substance at either end of the sarcomere passes into the pores of the sarcous element, so that the sarcomere becomes shorter and thicker. The shortening of the whole muscle is thus regarded as the result of the shortening of its sarcomeres.

When a living muscle is examined with polarised light the dim segments are seen to be doubly refracting (anisotropous), while the clear segments are singly refracting (isotropous).

In certain animals, such as the rabbit, some of the muscles are pale and others are red in colour. The pale muscles have the structure just described, whereas the red muscle fibres contain more sarcoplasm than the pale ones, and their nuclei are scattered throughout the substance of the fibres; the capillaries also show numerous small saccular dilatations. The red colour is due to the presence of hæmoglobin in the fibres. These muscles contract more slowly than the pale muscles, but their contraction is more prolonged. In many animals these two varieties of fibre are found together in the same muscle. All muscle fibres are supplied with nerve fibres, some of which are motor and end in the muscle fibres in end-plates, while others are sensory and convey impulses from the muscle to the central nervous system.

Chemical and Physical Characters of Muscle.—Muscle contains about 75 per cent. of water and 25 per cent. of solid substances, of which proteins form 18 to 20 per cent. The other constituents are a small amount of fat, glycogen ($\frac{1}{2}$ to 1 per cent.), inosite, and a number of nitrogenous extractives including creatine, xanthine, and hypoxanthine; the most important of these is creatine, which forms 0·2 to 0·4 per cent. of the muscle.

At a variable period after death the proteins coagulate, the product being called myosin, and the muscles become rigid and opaque; this condition is known as *rigor mortis.*

The nature of the proteins in fresh muscle can be studied if coagulation is delayed by cooling the muscle. The living muscle is minced at a temperature of 0° C., and is then extracted with ice-cold saline solution (0·9 per cent. NaCl) and filtered; the filtrate contains two proteins, namely paramyosinogen and myosinogen. The former is a globulin which coagulates at 47° to 50° C., and constitutes about 20 per cent. of the total protein in muscle. The remaining four-fifths consist of myosinogen, which has the characters of an albumin, though it coagulates at the low temperature of 56° to 60° C. When the solution

is warmed it clots, the proteins being converted into myosin, though the myosinogen passes through a transition stage as soluble myosin, which clots at 40° C.; in the frog's muscle soluble myosin is present as such in the living muscle. The coagulation of muscle plasma can be prevented by the removal of calcium salts, but there is no evidence that it is brought about by a ferment.

Resting muscle is very extensible and can be stretched by applying a weight to it; it is also feebly but perfectly elastic, and returns completely and rapidly to its original length when the weight is removed.

THE CONTRACTION OF VOLUNTARY MUSCLE.

In response to a stimulus a living muscle alters its form, becoming shorter and thicker; this change of form constitutes muscular contraction, and can be very easily studied in the muscles of the frog. For this purpose the gastrocnemius muscle and the sciatic nerve which supplies it are generally used, and are known as a muscle-nerve preparation. The fibres in the gastrocnemius do not run regularly from end to end of the muscle, and when it is desirable to use a muscle the fibres of which run approximately parallel to one another, the sartorius may be chosen. The muscle may be made to contract either by a mechanical stimulus such as a pinch, or by a chemical stimulus, for instance the application of acid or ammonia, or by an electrical current. On account of the ease with which its strength can be graduated, the electrical current is the most convenient of these artificial stimuli, and it may be applied either as a constant current or in the form of single or repeated induction shocks. The normal stimulus to muscular contraction during life is an impulse passing from the central nervous system along the nerve which ends in the muscle fibres. In a muscle-nerve preparation, the muscle contracts either when it is stimulated directly or when the stimulus is applied to the nerve.

It was formerly supposed that even when the stimulus was applied to the muscle itself the latter did not respond directly to the stimulus, but contracted because this acted upon the nerve fibres running within the muscle. There is no doubt, however, that muscle can be excited to contract independently of impulses reaching it along nerve fibres (independent irritability of muscle). Curare paralyses the endings of nerve fibres in muscle, and when it is injected into an animal stimulation of a motor nerve has no effect upon the muscle, whereas direct stimulation of the muscle causes it to contract.

The changes which take place in a contracting muscle are (1) a

change of form and physical condition, (2) an electrical change, (3) chemical changes, and (4) evolution of heat.

Changes in Form and Physical Condition.—These may be studied in the muscle-nerve preparation of a frog by fixing the upper attachment of the gastrocnemius muscle and attaching the tendo Achillis by a thread to the short arm of a lever; the long arm carries a writing point, and a weight can be attached to it if so desired. The muscle, when it contracts, pulls on the lever, and the movement of the writing point can be recorded on a smoked moving drum.

When a single induction shock of suitable strength is applied to the muscle, it responds by a single contraction or twitch. A graphic record of such a contraction is shown in fig. 2.

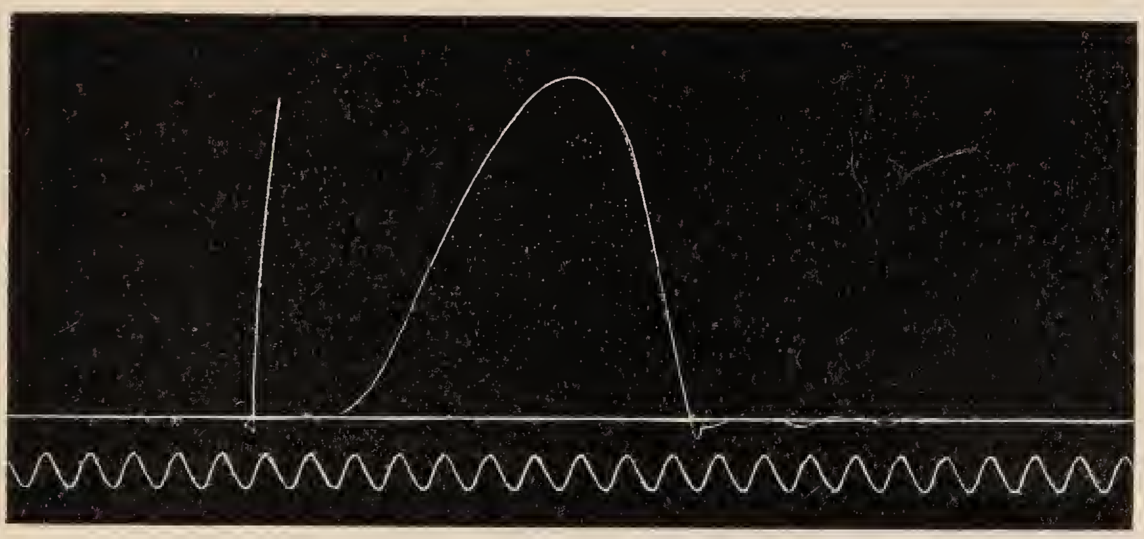


Fig. 2.—Simple muscle twitch.

The vertical line marks the moment at which the stimulus was applied. Below is a time-record, each double vibration representing $\frac{1}{100}$ second.

The contraction lasts about one-tenth of a second, and the tracing shows three parts, namely, (1) a short latent period, during which the muscle shows no visible change; (2) a period of shortening of the muscle, whereby the lever is raised; and (3) a period of relaxation, during which the muscle returns to its former length. The length of the latent period is due partly to the inertia of the lever and recording apparatus. This source of error can be avoided by interposing a muscle between a source of light and a rapidly moving photographic plate; the thickening of the muscle, when it contracts, is photographed, and the interval between the application of the stimulus and the beginning of contraction is measured. This interval, which is only 0·0025 second, represents the true latent period. The relaxation is not an active process, but is due to the weight of the lever pulling the muscle back to its former length; if an isolated muscle lying on mercury, and therefore not subject to any tension, is made to contract, it relaxes very imperfectly.

A certain strength of stimulus is necessary in order to produce any visible shortening of a muscle; a further increase in the strength of the stimulus, beyond this point, causes the muscle to contract more strongly, until finally the contraction becomes maximal. The varying degree of the response of the muscle to varying strength of stimulus is due to the fact that a weak stimulus affects only a few fibres, whereas a strong stimulus throws into contraction a large number of fibres; when all the fibres are stimulated, the shortening is maximal. Each fibre, however, if it contracts at all, gives the maximal contraction of which it is capable for the conditions under which it is placed, whatever the strength of the stimulus. This is known as the "all or none law," and holds good whether the muscle is stimulated directly or through its nerve.

When a muscle contracts, the contraction travels from the point of stimulation in the form of a wave at the rate of 5 to 6 metres per second in mammals and 3 to 4 metres in cold-blooded animals. This rate can be measured by resting two levers on a muscle, one at the middle, the other at one end, and applying a stimulus to the opposite end of the muscle. The lever nearer the stimulated point will rise earlier than the one at the opposite end of the muscle; and if this interval is measured and the length of muscle between the two levers is known, the rate at which the wave travels can be calculated. The length of the wave is measured by multiplying the rate at which it travels by its duration at any one point; it varies in frog's muscle from 150 to 300 millimetres.

A rise of temperature quickens, and a fall of temperature delays, every phase of the contraction. If the muscle is lifting a small load, the lever often rises higher at a high than at a low temperature, since the sudden jerk given to the lever by the rapid contraction imparts to it a greater momentum than when the pull on the lever takes place more gradually. On the contrary, when a heavy weight is attached to the lever, a slowly contracting cooled muscle may be more effective in raising the lever than the rapidly contracting warmed muscle. These differences are of purely mechanical origin, and the actual force of the contraction for a given load and for the same strength of stimulus remains unchanged between 5° C. and 20° C. Cooling increases the excitability of muscle, and maximal stimuli should therefore be used in studying the effect of temperature on the height of contraction. Prolonged exposure to a temperature of 0° C. destroys the vitality of muscle.

If a muscle is repeatedly stimulated, the height of the contractions diminishes, and all phases of the contraction, including the latent period, are prolonged; finally, the muscle may fail to contract in response to a stimulus. This condition constitutes fatigue.

When a weight is attached to the lever the height of the contraction diminishes as the weight is increased, until, finally, the muscle fails to raise the weight at all. The product of the weight raised, and the height through which it is lifted, represents the work done by the muscle; up to a certain point, an increase in the weight raised increases the work done by the muscle.

Contracting muscle differs from resting muscle in being more extensible and more elastic, that is, it returns to its original length more rapidly than resting muscle when the force stretching it is removed.

Isotonic and Isometric Curves.—When a muscle lifts a weight attached to a lever, the weight follows the movement of the lever, and the pull or tension which it exerts upon the muscle remains unchanged during the contraction; the curve thus obtained is called *isotonic*. The muscle may be made, however, to pull against a strong spring so that its length remains almost unaltered during its contraction, although it exerts a varying tension upon the spring; the minute movements of the spring are magnified and recorded photographically. In this case the contractile stress set up in the muscle varies throughout the contraction, though the length of the muscle undergoes no appreciable change. Curves thus obtained are called *isometric*, and resemble isotonic curves in their general form.

Tetanus.—If a second stimulus is sent into a muscle before the shortening caused by the first stimulus is at an end, the muscle shortens still further, this being called summation of effects. When the stimuli are rapidly repeated (fifty or more per second), the muscle contracts very strongly, and remains contracted so long as the stimuli are continued; the prolonged contraction is known as *tetanus*.

Constant Current.—When a constant current is passed through a muscle, it enters at one point called the anode, and, after traversing the muscle, leaves it at the kathode. When the circuit is completed, *i.e.* at the make of the current, the muscle gives a single twitch, and there is another twitch when the current is broken; during the passage of the current the muscle remains relaxed. The contraction taking place when the current is made starts at the kathode, whereas the contraction occurring at the break of the current starts at the anode. This can be observed by clamping a skeletal muscle in the middle and attaching a lever to each end; one electrode is placed on each half of the muscle. When the current is made, the portion of the muscle connected with the kathode contracts first, and the lever attached to this half of the muscle rises before the other lever. The same phenomenon is still more readily seen, and can be directly

observed, in slowly contracting muscles, such as the cardiac muscle of the frog.

Electrical Changes in Muscle.—When a constant current is passed into a muscle through metallic electrodes, electrolysis takes place in the muscle; the electrolytes accumulate near the electrodes, and give rise to a current which passes in the opposite direction to that in which the constant current is passing, and tends to neutralise the latter. This phenomenon is known as polarisation, and in recording the electrical currents occurring in muscle it is necessary to use non-polarisable electrodes.

The electrical currents in muscle may be observed by means of either the capillary electrometer or the string galvanometer. The

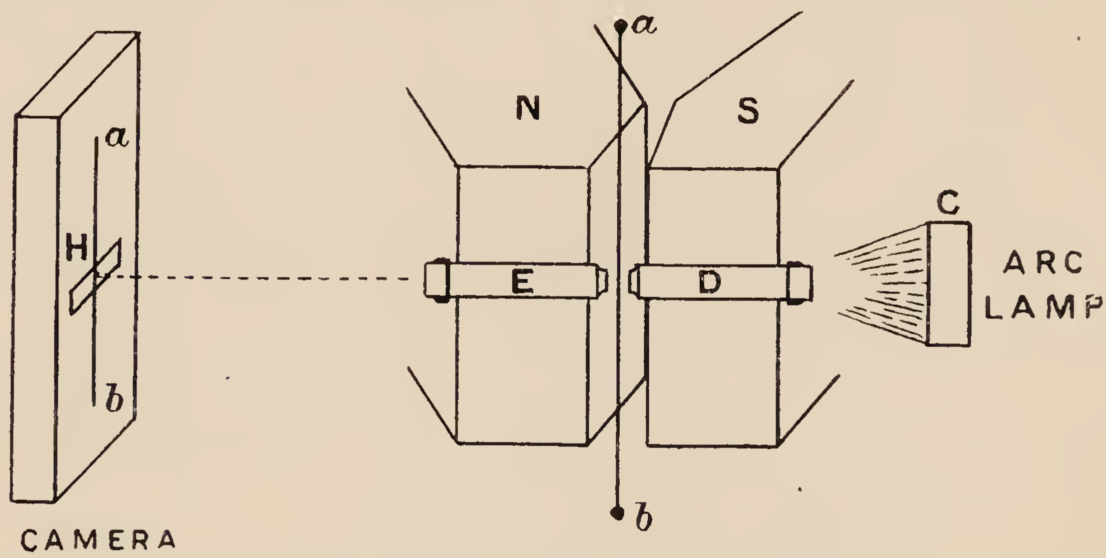


Fig. 3.—Scheme of string galvanometer.
a, *b* is the quartz thread; N and S are the electro-magnets; E is a microscope. The magnified image falls on the slit H, and is photographed. (Hume.)

capillary electrometer consists of a glass tube drawn out at one end to a capillary, and partly filled with mercury; the capillary tube opens into another tube containing 10 per cent. sulphuric acid. Two platinum wires pass, one into the sulphuric acid, the other into the mercury. When the electrometer is connected with two points of different potential, the mercury moves up or down the capillary tube. If the point connected with the acid is negative as compared with that connected with the mercury, the latter moves down towards the acid; if the point connected with the acid is positive, the mercury moves away from the acid. The movements are rapid and are proportional to the difference of potential between the two points under observation; they may be directly observed under the microscope, or may be recorded photographically.

The string galvanometer consists of a very delicate quartz thread, silvered over and hanging between two strong electro-magnets through which a current is passing; by means of terminals passing from each end of it, the thread can be connected with a muscle or other structure.

When a current passes through the thread, it is pulled towards one or the other magnet according to the direction of the current. The thread is illuminated by a strong light, and a magnified image of its movements can be thrown on a screen and observed directly; and if the screen is replaced by a moving photographic plate, these movements can be recorded.

When a perfectly uninjured muscle, *e.g.* the sartorius of a frog, is connected by means of non-polarisable electrodes at B and C (fig. 4), with the string galvanometer, no electrical current can be detected, and the muscle is said to be *isoelectric*. The application of a single induction shock at the point A causes a contraction travelling as a wave

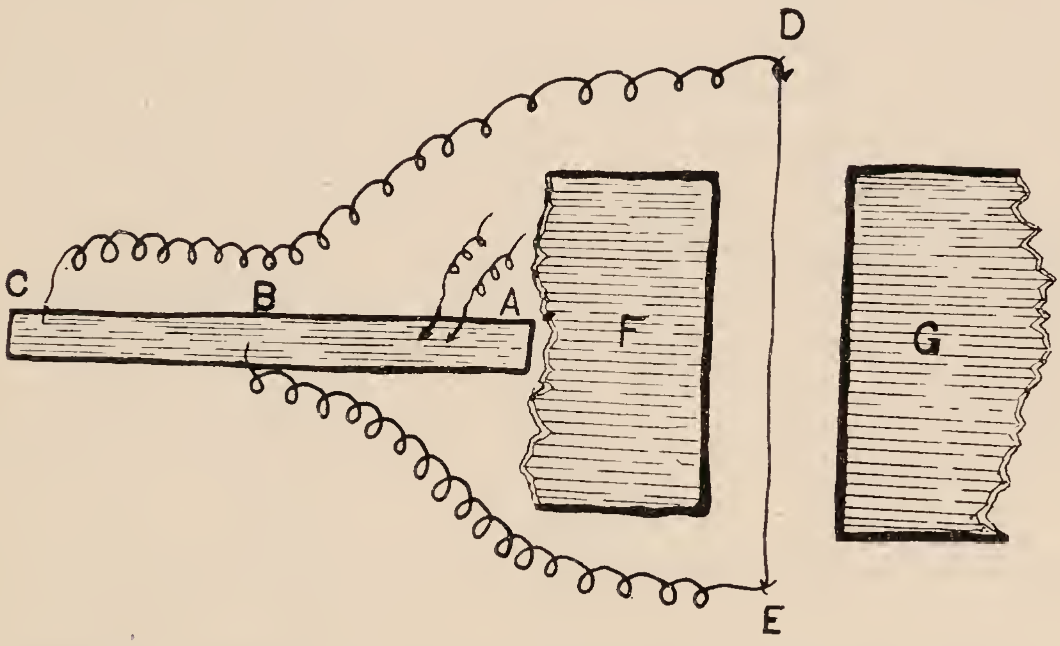


Fig. 4.—Diagram to show the method of investigating electrical changes in muscle. D, E is the thread; F and G are the electro-magnets of the string galvanometer.

from A to C, and at the same time an electrical change is recorded by the galvanometer.

The stimulus produces a chemical change, which travels along the muscle at the same rate as, and which precedes, the wave of contraction. As this wave of excitation passes along the muscle, it gives rise to an electrical change of such a kind that the excited part of the muscle is negative to the resting part. The electrical changes also precede the mechanical shortening of the muscle; they take place chiefly during the latent period, and are completed long before the contraction is over.

Since excited muscle is negative to resting muscle, the electrical change is diphasic, as is shown diagrammatically in fig. 5. The first movement of the thread (represented by the ascending part of the curve in the figure) occurs when the muscle at B is excited, and becomes negative to the resting muscle at C; the current flows through the

galvanometer from C to B. When the excitatory process reaches C, and is still present at B, there is no electrical current and the thread swings back to its original position. This period is extremely short, and almost immediately the excitatory process passes off at B, though it is still present at C; the point C is now negative to B and the thread swings once more, this time in the opposite direction. Finally the whole muscle ceases to be excited and the thread returns to its resting position. This diphasic current is known as the *current of action.*

If the muscle is injured at the point C, a current flows through the galvanometer from B to C even when the muscle is resting, and is called the current of rest or injury. If the muscle is thrown into contraction, the point B becomes electrically negative as compared with its resting state, and then returns to its former condition; the injured muscle at C does not contract and its electrical condition remains unchanged. The record of the galvanometer therefore shows a single (monophasic) deflection. Since the current of action in this case flows in the opposite direction to that of the injury current, it is often spoken of as the negative variation of the injury current.

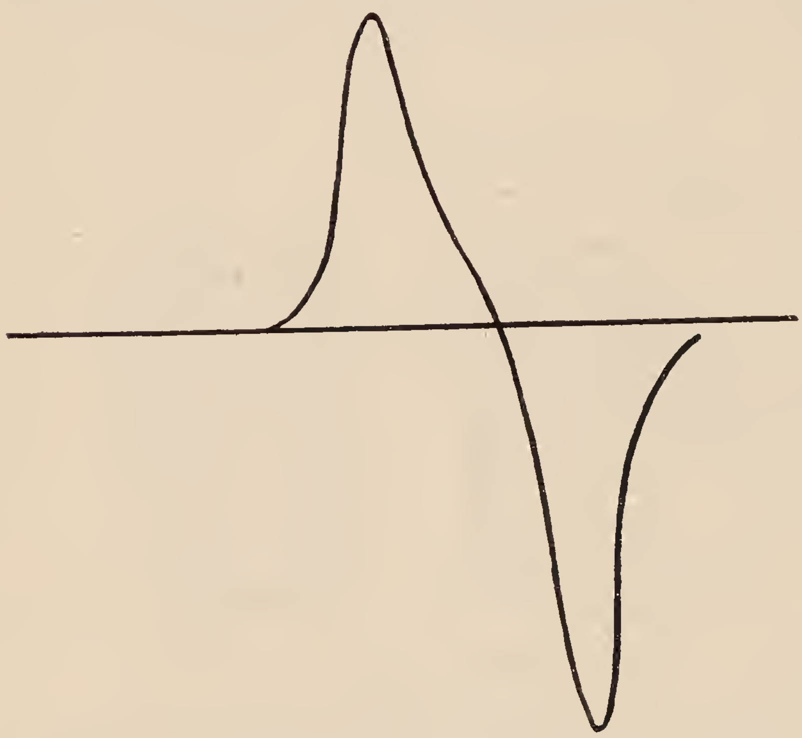


FIG. 5.—Diphasic electrical change in muscle (diagrammatic).
The horizontal line represents the position of the thread when at rest.

Thus it is evident that both injured and contracting muscle are negative to normal resting muscle. These changes are abolished by the death of the muscle, and are thus bound up with the chemical changes taking place in a contracting or injured muscle. They are independent, however, of the mechanical shortening, and still occur in an excited muscle even when its power to contract is abolished by steeping it for a short time in distilled water.

Although it is customary to speak of excited muscle as "negative" to resting muscle, it must be remembered that it is really electropositive to the resting muscle; in the same way, zinc is the electropositive element in a battery. The term "negative" simply means that the current passes through the galvanometer towards the excited

tissue, and has no reference to the actual electrical condition of this tissue.

The electrical changes in muscle can also be demonstrated without the aid of a galvanometer. Two muscle nerve preparations are made, and the nerve of one preparation A is brought into contact at two points with the muscle of the other preparation B. When the muscle of B contracts, the current of action set up in it acts as a stimulus to the nerve of A; this stimulus is conducted to the muscle of A which is thrown into contraction.

Chemical Changes during Contraction.—Living muscle is constantly taking up oxygen from the blood and giving off carbonic acid. During contraction it takes up more oxygen and gives off more carbonic acid, and at the same time heat is evolved and lactic acid is formed. The production of acid during muscular contraction can be readily demonstrated in a frog's muscle-nerve preparation; if the muscle is made to contract vigorously for a few minutes it becomes acid to litmus paper. Another method of illustrating the same fact consists in injecting into the dorsal lymph sac of a frog a solution of acid fuchsin, which is colourless in neutral and red in acid solution. When one gastrocnemius muscle is made to contract an hour or two after the injection, the contracting muscle becomes red, whereas the resting muscles are not coloured.

It can be shown that the acid formed is lactic acid by means of Hopkins' test.

A few drops of an alcoholic extract of muscle, two or three drops of a saturated solution of copper sulphate, and 5 c.c. of strong sulphuric acid are mixed in a test tube and placed in boiling water for a minute or two. The fluid is cooled and a few drops of alcoholic thiophene solution are added; on warming the solution, a cherry red colour develops if lactic acid is present.

In all probability, when a muscle contracts the first chemical change taking place is the breaking down of a compound of dextrose with some other substance the nature of which is unknown, the decomposition resulting in the formation of lactic acid; in the presence of an adequate supply of oxygen, the lactic acid can be subsequently oxidised to carbonic acid and water according to the following equation :—

$$\underset{\text{lactic acid}}{C_3H_6O_3} + 3O_2 = 3CO_2 + 3H_2O.$$

This is shown by the observation that an isolated frog's muscle, when made to contract in an atmosphere free from oxygen, gives off less carbonic acid and contains more lactic acid than when it contracts in an atmosphere containing oxygen. Further, if a muscle which

contains lactic acid is exposed for some hours in pure oxygen, the amount of lactic acid in it decreases. Evidently the muscles possess the power of destroying lactic acid.

This process also takes place in the living animal, but if the supply of oxygen to the muscles is deficient, *e.g.* during asphyxia, or if the formation of lactic acid is very rapid, for example in actively contracting muscles, the acid is not completely oxidised and passes into the blood and may be excreted in the urine. In man the excretion of lactic acid in the urine is 3 to 4 mgr. per hour during rest; and this may be raised by severe exercise to 400 mgr. or more hourly. Hence the appearance of lactic acid in increased amount in the blood and urine may be taken as evidence that the supply of oxygen to the muscles is either absolutely or relatively deficient. Owing to the passage of lactic acid into the circulating blood, the muscles themselves do not become acid in reaction even after severe exercise, though it is said that the muscles of animals hunted to death are acid.

It is probable that part of the lactic acid is not oxidised, but is synthesised again by the muscles into the carbohydrate compound by the decomposition of which it was originally formed.

The chemical changes taking place in contracting muscle are not confined to the process just described, and the oxidation of carbohydrate, fat, and protein is also increased during muscular activity.

Heat Production in Muscle.—During muscular contraction heat is produced, and the contraction of a large number of muscles, such as occurs during muscular exercise, may be sufficient to raise the temperature of the whole body one or two degrees. The heat produced in a small isolated muscle during a single contraction cannot be measured by a thermometer, but is usually determined by means of a thermopile, which consists of a junction between two metals, the metals being connected with a galvanometer. When the junction is heated, an electrical current is set up and passes through the galvanometer. In the more recent forms of thermopile the metals used are copper and an alloy called constantan, and the thermopile may consist of a large number of such junctions, which are connected with a string galvanometer. A muscle, such as the frog's sartorius, is placed in contact with these junctions, and can be made to contract by sending a current through electrodes placed one at each end of the muscle. The muscle is fixed at one end and attached at the other, either to a recording lever or to a spring, whereby the tension on the muscle can be varied or the changes in contractile stress occurring during its isometric contraction can be studied. Any production of heat in the muscle gives rise to a current through the thermopile, and

to deflection of the thread of the galvanometer; the amount of deflection produced by a unit of heat is previously determined.

Experiments made with this apparatus show that the production of heat in muscle occurs both during and for some time after its contraction.

(1) When a muscle contracts, a certain amount of potential energy is liberated as free energy, which can be used in the carrying out of work, or can be evolved as heat, or may be manifested partly as work and partly as heat. The amount of the energy set free and available for this purpose depends upon the initial length of the muscle fibre.

If the muscle is stretched by a spring or weight, the energy set free and the contractile stress, that is, the force with which the fibres tend to contract, are greater than when it is not stretched. The proportion of the energy thus set free, which appears as work or as heat respectively, depends upon the mechanical conditions under which the muscle is placed. If the muscle is allowed to lift a weight, it does work which is measured by the product of the weight raised and the height through which it is lifted; and if the mechanical conditions are favourable, the greater part of the energy set free during the contraction may appear as work. If the muscle is not allowed to contract and to do work, the whole of the energy set free during the contraction appears as heat.

(2) After the contraction is over, a further evolution of heat takes place, which is due partly to the oxidation of lactic acid, and partly also to the rebuilding of the precursor of lactic acid, the energy needed for this process being supplied by the oxidation of other substances in the muscle with the liberation of heat and of carbonic acid.

The efficiency of muscular contraction is the proportion of the total energy set free during and just after the contraction, which appears as work. The mechanical conditions under which muscular contraction takes place in the body are usually such that the efficiency is comparatively constant; in man, from 20 to 28 per cent. of the total energy set free during muscular contraction appears as work.

Fatigue and Rigor Mortis.—When a muscle passes into rigor mortis it shortens slightly, becomes rigid and opaque, and loses its elasticity and extensibility. During its passage into rigor the muscle becomes acid, the acid formed being lactic acid, and heat and carbonic acid are evolved.

These changes are all due to the breaking down of the carbohydrate precursor of lactic acid. In this process heat is evolved, and the lactic acid reacts with the sodium carbonate in muscle, setting free carbonic acid, which is given off. When the amount of lactic acid formed in the

muscle attains a certain level, the proteins are coagulated and the physical characters of the muscle are altered. It is for this reason that the muscles in fatigued animals pass into rigor mortis more rapidly after death than the muscles of resting animals, since at the time of death they already contain some lactic acid. That the accumulation of lactic acid in muscle can cause fatigue is shown by the fact that the contraction characteristic of fatigued muscle can be induced in the fresh muscle by perfusing it with blood containing lactic acid. Fatigue is thus brought about in part by the same cause as that which ultimately leads to rigor mortis; but the larger amount of acid produced in the latter brings about an irreversible change in the proteins, causing the death of the muscle, whereas the acid is gradually removed from a fatigued muscle, which is thus restored to its normal condition.

When a muscle is repeatedly stimulated through its nerve, it gradually becomes fatigued and finally fails to contract. When this point is reached the muscle will still contract, if directly stimulated, so that its failure to contract when stimulated through its nerve must be due to fatigue of either the nerve trunk or the nerve endings. It can readily be shown that it is the nerve endings which become fatigued in such an experiment.

Two muscle nerve preparations are made, and the nerves are continuously stimulated with a tetanising current, the passage of the stimulus to one muscle being prevented by cooling a small portion of the nerve near the muscle to 0° C.; in this way both nerves are stimulated, but only one muscle is thrown into contraction. After a short time the muscle which is contracting becomes fatigued and fails to contract. The cooled nerve is then warmed, the stimulation being continued, and the muscle of this preparation at once contracts vigorously. Since both nerve trunks have been equally stimulated, it is evident that the fatigue does not lie in the nerve trunks and must therefore have its seat in the nerve endings.

Experiments of this kind have shown that both medullated and non-medullated nerves are practically incapable of fatigue, and even after six hours of continuous excitation the nerves are just as excitable as at the outset.

VOLUNTARY CONTRACTION.

The contraction of a muscle under the influence of the will is much longer than a single twitch and represents a short tetanus, since even the quickest movement which an individual can carry out voluntarily lasts at least one-tenth of a second, and usually longer. The nature of voluntary movement has recently been demonstrated by recording the

electrical changes occurring during a voluntary contraction. Using the string galvanometer, about 50 electrical variations per second can be observed in the contracting muscle; and if the electrical variations of a motor nerve during a voluntary or reflex contraction of the muscle which it supplies are similarly recorded, it is found that about 50 impulses per second are passing along the nerve. When a skeletal muscle is stimulated 50 times a second it passes into tetanus; and it may be concluded that voluntary muscular contractions are almost always tetanic in character, and are brought about by the discharge of rapidly repeated impulses from the cells of the central nervous system.

UNSTRIATED MUSCLE.

The muscle fibres which occur in the walls of the digestive tract, blood-vessels, and other organs show no transverse striation and are called plain or involuntary muscle fibres. Each fibre is spindle-shaped and has an oval nucleus; its cell substance frequently shows a delicate longitudinal striation. The fibres are united to one another by a cement substance which can be stained with silver nitrate.

The changes taking place in smooth muscle, when it contracts, differ in many respects from those occurring in skeletal muscle. In the first place, the duration of the contraction is very prolonged; the latent period may be from 0·2 to 0·5 second, and the contraction may last for two or three minutes. Secondly, the muscle is much more easily excited by a constant current than by induction shocks, and frequently fails to give any response to a single induction shock. Owing to the slowness of the process, the origin of the contraction at the kathode when a constant current is made, and at the anode when the current is broken, can be observed with great ease.

Thirdly, smooth muscle shows a great tendency to contract rhythmically, the rhythm being most easily evoked when the muscle is stretched. The effect of tension is often well seen in the hollow organs whose walls are partly composed of smooth muscle. If such an organ is rapidly distended by the injection of fluid, the sudden tension placed on the muscle fibres in its wall causes them to contract forcibly, the contraction being sometimes continued in a rhythmic manner for a short time. Smooth muscle is also susceptible to chemical stimuli and can be thrown into contraction by substances such as barium salts.

One of the most characteristic features of smooth muscle is its power to remain in a state of partial contraction or tone, even after it is cut off from any connection with the central nervous system. Stimulation of the nerves to the muscle may bring about either an increase or a decrease of this tone; and most unstriated muscles have

a double nerve supply, one set of nerves when stimulated causing contraction, and the other relaxation of the muscle.

CILIARY MOVEMENT.

Cilia are delicate filaments projecting from the border of columnar epithelial cells, and are found in the greater part of the respiratory passages, in the generative organs, and elsewhere.

Their movement consists in a rapid bending of each cilium, followed by a slow return to the erect position. All the cilia on a ciliated surface bend in the same direction, the movement travelling as a wave over the surface. The movements are repeated ten to twelve times a second, and serve to carry forward solid particles of dust or mucus in the respiratory passages; in the Fallopian tubes they assist the passage of the ovum.

Ciliary movement is entirely independent of the central nervous system, and its mode of production is unknown.

CHAPTER IV.

NERVE FIBRES.

The nerve fibres form the medium by which the various structures of the body are brought into communication with the central nervous system, and thus indirectly with each other. The fibres for the most part leave the central nervous system in bundles which are bound together to form nerve trunks. The nerve trunks give off branches in their course, the ultimate ramifications consisting of individual fibres.

Nerve fibres are of two kinds, medullated and non-medullated. A medullated nerve fibre is a cylindrical structure and consists of the nerve fibre proper, known as the axis cylinder, surrounded by two sheaths. The outer sheath is a transparent structureless membrane called the neurolemma. The inner sheath is thicker, and is composed of a refractive material of a fatty nature, called myelin. The myelin sheath is interrupted at regular intervals, the interruptions being known as the nodes of Ranvier. About midway between each two nodes of Ranvier a nucleus is found, lying under the neurolemma and surrounded by a small quantity of protoplasm.

A non-medullated nerve fibre consists of axis cylinder and neurolemma with nuclei, and has no myelin sheath.

The axis cylinder of a nerve fibre is a process of a nerve cell, usually the process known as the axon. It consists of an aggregation of fine fibrils, imbedded in an interfibrillar fluid material.

In the nerve trunks the fibres are bound together in cylindrical cords or funiculi, each of which is enclosed in a sheath of dense connective tissue, the perineurium. The funiculi are held together in the nerve trunk by looser connective tissue, the epineurium. Both medullated and non-medullated nerve fibres are usually present in a nerve trunk, such as is found in the limbs.

When a nerve fibre is traced to its peripheral termination it is found to end either in free fibrils or in a special end-organ. Free fibrillar endings occur in the epithelium of the skin, around special sensory cells, such as those of the taste buds and of the organ of

hearing, around gland cells and in other situations. Terminations in special end-organs are found in the touch corpuscles of the skin and in the end-plates in striped muscle fibres.

The chief chemical constituents of nerve fibres are protein, nucleo-protein, lecithin, and cholesterol. The myelin sheath of medullated fibres is mainly formed of lecithin.

THE FUNCTION OF NERVE FIBRES.

Nerve fibres have one function only, that of the conduction of impulses. Generally speaking, any one nerve fibre conducts in one direction only, and the fibres are classified as efferent and afferent, according as they conduct impulses away from or towards the central nervous system. The direction in which an impulse normally passes along a nerve depends upon the connections of the fibres and not upon a property of the fibres themselves, these being in reality capable of conducting in either direction. Thus in a motor nerve fibre the excitatory process originates in the central nervous system and is propagated towards the muscle, and in a sensory nerve the excitatory process is set up in the nerve-ending, for example in the skin, and is propagated towards the nerve centres.

The function of nerve fibres has been studied chiefly by means of artificial stimuli, mechanical, thermal, electrical, and chemical, motor nerve fibres being generally used for experiment because the propagation of an impulse in a motor nerve is easily demonstrated by the resulting muscular contraction. Two other phenomena accompany or follow the propagation of a disturbance along a nerve: (1) an electric response, and (2) the occurrence of a refractory period. (1) The electric response is detected by the use of a galvanometer, and consists in a brief wave of negativity which accompanies the disturbance, the excited part of the nerve being negative to the resting part. (2) The refractory period follows immediately the passage of the disturbance, and lasts about one-thousandth of a second. During that period a second stimulus applied to a motor nerve fails to excite a muscular contraction.

In the study of the function of nerve fibres two points have to be considered, the excitatory process and the propagation of the resulting disturbance.

The Excitatory Process.—Nothing is known as to the physico-chemical nature of the normal excitatory process. A similar condition may, however, be set up artificially in various ways. For example, cutting or pinching a motor nerve, or the sudden application to it of heat, or dipping it in strong salt solution or in glycerol, or the

application to it of electrical stimuli, will be followed by contraction of the muscle with which it is connected. The most convenient form of stimulus for experimental purposes is the electric current.

Induced Current.—Induced electricity is generally used for purposes of stimulation, because its strength can be easily controlled and also because of the brief duration of the current. When a single induction shock of sufficient strength is applied to the nerve of a muscle-nerve preparation, (1) an excitatory process is set up in the nerve at the point stimulated, (2) a disturbance arising at that point is propagated along the nerve to the muscle, and (3) the muscle contracts.

Constant Current.—If a length of nerve is introduced into the circuit of a constant current, an excitatory process is only set up in the nerve, as in muscles, when the circuit is made or broken, and not during the passage of the current. The passage of the current is nevertheless accompanied by changes in the excitability, conductivity, and electromotivity of the nerve, which together constitute the condition known as electrotonus. The changes in excitability may be shown in the nerve of a muscle-nerve preparation from the frog. The nerve is laid upon a pair of non-polarisable electrodes connected with a galvanic cell, a reverser being introduced into the circuit. The electrodes from an induction coil are applied to the nerve between the non-polarisable electrodes and the muscle. The position of the induction coil which gives a minimal effective stimulus is found before the constant circuit is made, then the key of the latter is closed, and the stimulus from the induction coil is repeated. If the positive pole or anode is the nearer to the stimulating electrodes, the stimulus will now be ineffective, because the stimulated area of the nerve is in a condition of anelectrotonus or reduced excitability. If the direction of the constant current be reversed, repetition of the stimulus will give a maximal contraction of the muscle, because the stimulated area is in a condition of kathelectrotonus or increased excitability. Associated with this electrotonic variation in excitability is the fact that, as already pointed out in connection with the stimulation of muscle, the excitatory process set up by the closing of a constant circuit occurs at the kathode, and that set up by breaking the circuit at the anode. In other words, the excitatory process is produced by the setting up of kathelectrotonus and by the resolution of anelectrotonus.

The Propagated Disturbance.—The propagation of an impulse along a nerve may be demonstrated by the effect produced in an organ, such as muscle, or by recording the electric response by means of a capillary electrometer or string galvanometer. For the latter purpose the nerve is included in the galvanometer circuit, non-polarisable electrodes

being used. A single induction shock is applied to the nerve at a distance from the non-polarisable electrodes, and the movement of the mercury in the capillary electrometer or of the string of the string galvanometer is photographed on a rapidly moving plate. In this way it is shown that the part of the nerve which is excited at any instant is negative to all other parts of the nerve.

By recording the electric response, it can be shown that when any part of a nerve is stimulated the disturbance is propagated in both directions. If the middle of a length of nerve is stimulated by a single induction shock, each end of the nerve being in circuit with a galvanometer by means of non-polarisable electrodes, both galvanometers record the passage of a current of action. Apart from the electric response, the changes produced in a nerve by the passage of an impulse are very slight. No appreciable production of heat can be detected by the most delicate thermo-electric methods. Chemical changes must take place, because the nerve fibres lose their irritability when completely deprived of oxygen, and the loss of irritability occurs more rapidly if the nerve is stimulated; but the true nature of the chemical changes is unknown. Possibly the changes which occur during the propagation of the disturbance are largely physical, and depend upon changes of surface tension.

The Velocity of a Nervous Impulse.—The rate at which an impulse is transmitted in the nerve of a frog may be measured by using a muscle-nerve preparation and recording the contraction of the muscle on a rapidly moving drum or pendulum myograph, (1) when the stimulus is applied as far as possible from the muscle, and (2) when it is applied close to the muscle. The two tracings are recorded on the same abscissa, the point of stimulation being at the same point of the tracing for both. The difference in latent period is measured by means of a time tracing taken from a tuning-fork giving 250 double vibrations per second. This difference gives the time taken by the impulse to travel along the length of nerve between the two points stimulated. In the case of frog's nerve the rate of transmission is found to be about 28 metres per second. In human nerves it is estimated to be about four times this rate.

Conditions which affect Excitability and the Propagation of the Disturbance in Nerve.—It has already been pointed out (p. 30) that nerve fibres cannot be fatigued. Their excitability and conductivity may, however, be affected by temperature, drugs, and the passage of a constant current, as well as by the passage of a previous impulse along the nerve, and by injury.

Generally speaking, the irritability of nerve for induction shocks is

increased by a rise of temperature, and diminished by cooling. With currents of longer duration the converse effect is obtained, within limits, the excitability being increased by cooling the nerve because by the fall of temperature the subsidence of the excitatory process is delayed, although at the same time the initiation of a propagated disturbance is hindered.

The effect of volatile drugs on nerve is tested by enclosing a length of the nerve to a muscle in a glass tube which is made air-tight, and filling the tube by a side connection with the vapour of the drug to be tested. Carbonic acid gas and ether abolish both the excitability and conductivity of nerve, the excitability being the earlier to disappear. If the gas or vapour be replaced by pure air, the nerve returns to its normal condition, conductivity returning before excitability. Chloroform acts on nerve in the same way as ether but more powerfully, recovery being incomplete or not occurring at all when the drug is replaced by air.

The effect of the passage of a constant current on the excitability of nerve has already been described. The effect on conductivity is fairly parallel with that on excitability.

The refractory period which follows the stimulation of a nerve is a result of the passage of the propagated disturbance, and not merely a local condition of depressed excitability following the excitatory process. This is proved by sending the second stimulus into the nerve at a different point from the first, in which case the refractory condition is found to be the same as when the second stimulus is applied at the same spot as the first. The refractory state does not end abruptly, but passes off gradually, so that there is a gradual fall in the strength of the stimulus required to produce the second response.

Electrotonic Currents in Nerve.—Reference has already been made to the fact that the electromotivity of nerve is altered by the passage of a constant current. Uninjured nerve is isoelectric. If, however, a nerve is injured, as, for example, by division of its fibres, and is connected with a galvanometer by means of non-polarisable electrodes, one of which is applied to the injured area, and the other to the uninjured surface, a current, the so-called demarcation current or current of injury, will flow through the galvanometer from the uninjured surface to the injured part; that is, within the nerve itself the injured part is electro-positive to the uninjured. If a constant current ("polarising current") be passed through a part of the nerve, non-polarisable electrodes being used, the demarcation current will be increased at the anode, where the polarising current enters the nerve, and diminished at the kathode. Electrotonic currents are set up in

the nerve which have the same direction as the polarising current. These electrotonic currents are due to ionisation of the electrolytes which occur in solution between the electrode and the axis cylinder. Negatively charged ions are attracted to the anode, with a resulting concentration of ions which are positively charged on the axis cylinder near the anode. In the same way, negatively charged ions accumulate on the axis cylinder close to the kathode. The electrotonic currents are caused by the differences of potential thus produced.

Electrotonic currents in a nerve can produce the excitatory process in another nerve in contact with the first. If the nerve of a muscle-nerve preparation be laid on a second nerve which is stimulated by single induction shocks, each stimulus sets up electrotonic currents in the stimulated nerve, and these, setting up an excitatory process in the other nerve, lead to contraction of the muscle.

CHAPTER V.

THE CENTRAL NERVOUS SYSTEM.

SECTION I.

THE essential characteristic of life is the power of reaction to a stimulus, and in the higher animals this reaction is effected through the central nervous system, and constitutes reflex action. The life of the individual is to a large extent made up of a long series of reflex acts, varying in complexity, and carried out in response to stimuli arising in the outer world or within his own body.

In response to external stimuli, the animal acts as a whole and carries out movements directed to attack or defence, to the procuring of food, and the like; in response to internal stimuli, the activities of the different organs of the body are co-ordinated in such a way that the individual behaves as such and not as a group of independent organs.

Instances of this nervous control will be referred to in connection with the work of the heart, the function of respiration, the production of the digestive juices, and the other functions which are concerned with animal life.

But the activities of the central nervous system are not limited to the management of these vital processes. In addition, the central nervous system is the seat of those processes which are concerned with conscious existence. Impressions are conveyed to the brain from the outer world, and give rise to sensations of smell, taste, hearing, sight, and touch, and these in their turn call forth emotions, such as pleasure or pain. The activities of the central nervous system find expression in muscular movement, resulting in locomotion, speech, writing, or gesture. In the study of the various nervous functions, the science of Physiology has to deal with the mechanism by means of which afferent impressions are received and conducted to the nerve centres, with that by which they are associated in these centres, and with the further mechanism by means of which efferent impulses are transmitted

to the active tissues of the body. The consideration of the mental processes and the emotions is the province of the sister science of Psychology.

The nervous system consists of the brain and spinal cord (spinal medulla), with the nerves by means of which these central organs are connected with the other structures of the body. Microscopic examination of the brain and spinal cord shows that they are built up of nerve cells and nerve fibres, supported by a special form of connective tissue called neuroglia.

The nerves contain nerve fibres only, held together by ordinary connective tissue. Every nerve fibre, however, is a process of a nerve cell; and if a nerve fibre is divided, the part which is no longer in connection with the nerve cell undergoes degeneration. The histological unit of the nervous system is therefore the nerve cell with its processes, and this unit is known as a neuron.

The Neuron.—Every neuron consists of a nerve cell, known as a cyton, and its processes. In the simplest form the cyton is bipolar, with one process connected with each pole. Examples of this type are found in the spinal ganglia of fishes and in the ganglion on the auditory nerve in man. A modification of this form occurs in the human spinal ganglia, the two processes becoming fused together for a short distance in the course of development, so that the cell is histologically unipolar, though physiologically it is still a bipolar cell. A third form is multipolar, there being more than two processes connected with each cell. One of these processes is unbranched, and is known as the axon; the others are branched, and are called dendrons. The neurons which enter into the structure of the brain and spinal cord belong to the multipolar type, varying however in the shape of the cyton, the number and character of the dendrons, and the length of the axon in different regions.

The *cyton*, although differing in shape and size in different regions, is always distinguished by certain definite characteristics. It is usually large as compared with other cells, varying in diameter from 20 to 100 μ. It possesses a large, spherical nucleus which contains little chromatin, and within the nucleus a well-marked nucleolus. The cell substance is distinguished by the presence of certain bodies known as Nissl spindles and also by having delicate fibrils running through it. The Nissl spindles are granular aggregations in the form of minute spindles, as the name implies, are arranged more or less concentrically in relation to the nucleus, and stain well with methylene blue or toluidin blue. They appear to consist mainly of nucleoprotein, and also contain some iron. They are found in all parts of the cyton and in the basal parts

of the dendrons, but not in the axon hillock, the part of the cell from which the axon takes origin. The fibrils run through the cell from dendrons to axon, and, with some interfibrillar material, form the substance of the latter structure. Many nerve cells have a well-marked lymph capsule surrounding them.

The *axon* is, as has been said, a fibrillar structure, and usually becomes the axis cylinder of a nerve fibre, acquiring a myelin sheath soon after leaving the cyton. Axons are of variable length, the longest being those which extend from the lumbar region of the spinal cord to the foot. They do not branch as the dendrons do, but those which run a course in the central nervous system give off delicate twigs at right angles to their course, known as *collaterals*. Each axon ends by a terminal arborisation, either in relation with the cyton or dendrons of another neuron or in relation with muscle fibres or gland cells. The termination in connection with striped muscle frequently enters into the formation of a special form of nerve-ending known as an end-plate. The axons of certain cells in the central nervous system, belonging to what is known as Golgi's second type, are very short, do not acquire a myelin sheath, and form their terminal arborisation in relation with the cell body of a neighbouring neuron.

Dendrons are found in their most typical form in the neurons of the brain and spinal cord. They branch in a tree-like manner, and the branches frequently exhibit minute enlargements or projections. The dendrons are short as compared with the axon, and never extend any distance from the cyton.

The processes of nerve cells do not anastomose, but come into relationship by the more or less intimate mingling of the terminal arborisation of the axon of one neuron with the dendrons or cyton of another neuron. Such a communication, in which there is contact without continuity, is called a *synapse*. The contact is possibly not direct, the transmission of impulses from one neuron to the other being effected through an intermediate layer of some substance which does not form part of either neuron.

In addition to the fibrils which have been described as occurring in the substance of each nerve cell, an extracellular network of fibrils has been described, but it has not been established that there is continuity between the two networks. A third fibrillar network has been demonstrated, chiefly in invertebrate animals, which is said to be continuous from neuron to neuron, and, on the basis of this description, a theory has been put forward that nerve impulses are transmitted through the central nervous system by means of a continuous network of fibrils and not by a series of synapses. The evidence upon which

this theory of continuity rests, however, is at present insufficient to justify its adoption.

The Function of the Neuron.—The type of neuron which is most easily studied in the mammal is the unipolar form found in the ganglia on the posterior roots of the spinal nerves. As has already been pointed out, these cells are functionally bipolar, the single process resulting from the fusion of the two poles, and the two processes separate at some little distance from the cell, one passing towards the spinal cord and the other towards the periphery. Each becomes the axis cylinder of a medullated nerve fibre, but that which has a centrifugal course is functionally homologous with the dendrons of the neurons of the central nervous system. If either of the two processes is cut off from the cyton, it degenerates, while the portion left in connection with the cell body undergoes no obvious change. It may therefore be assumed that the cyton governs the nutrition of all parts of the neuron. Moreover, when one of its processes has been divided in this way, so that the normal function of the neuron is interfered with, changes occur in the substance of the cyton itself. The Nissl spindles undergo disintegration, so that the cell stains diffusely with methylene blue (fig. 6). This change is known as *chromatolysis*, and it indicates that the Nissl bodies are concerned in some way with the functional activity of the neuron. Further evidence in support of this conclusion is afforded by the fact that the Nissl bodies of the cells of the central nervous system diminish in number after an animal has been in active exercise. Chromatolysis also occurs as a result of the action of certain poisons, in fevers, and in asphyxia.

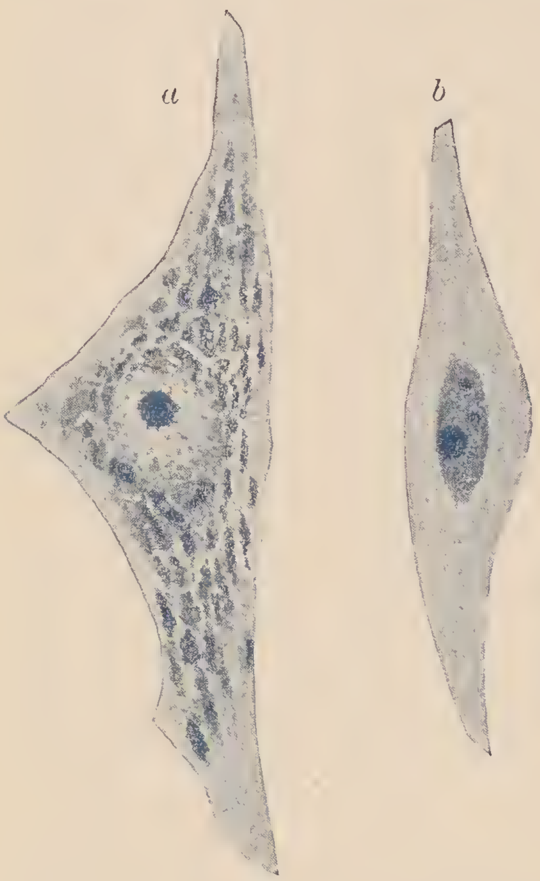


Fig. 6.—Two motor nerve-cells from the dog. (Photographed from preparations by Dr Gustav Mann.) From Schäfer's *Essentials of Histology*.

a, normal; *b*, after a period of prolonged activity.

Conduction of an impulse in a neuron takes place in one direction only. In the case of the fibres of the posterior spinal nerve roots, the conduction is from the periphery to the central nervous system. The anterior root fibres, on the other hand, conduct from centre to periphery. They are the axons of multipolar nerve cells which lie in the grey matter of the spinal cord. If the posterior root be divided

between the spinal cord and the ganglion, stimulation of the peripheral portion will have no result, either as regards sensation or muscular or glandular activity. Stimulation of the central portion will, however, be followed by sensation, and may result in reflex muscular movements. If the anterior root be divided, stimulation of the peripheral portion will be followed by muscular movements, while stimulation of the central end will give rise neither to sensation nor reflexes. In the production of a simple reflex by stimulation of the central end of the divided posterior root, the impulse passes from the terminal arborisation of the fibre or of its collaterals in the grey matter of the spinal cord across a synapse to the dendrons of a second neuron, the axon of that neuron passes it on to the dendrons of one or more of the multipolar cells the axons of which constitute the anterior nerve roots, and the impulse, altered in character, is thus transmitted to the responding muscles. There is thus a law of conduction, called the "law of forward direction," according to which an impulse will pass across a synapse from the axon of one neuron to the dendrons of another, but not in the reverse direction.

The Function of the Cell.—In a reflex action the afferent impulse is usually greatly modified in its passage through the central nervous system. For example, the comparatively slight stimulus of a crumb in the larynx may be followed by violent coughing, accompanied by contraction of other muscles besides those concerned with expiration. Again, when a reflex movement is excited by stimulation of an afferent nerve, the impulses travelling along the efferent nerve have a rhythm which is independent of that of the exciting stimulus. It was formerly thought that these and other modifications of the impulses in the nervous system were brought about by the nerve cell. It has been shown, however, in certain invertebrates that reflex action can still take place for a short time when the cells associated with the fibres forming the reflex arc have been destroyed. This and other similar observations indicate that the characteristic features of reflex action must be attributed not to the nerve cell but to the synapse. The function of the nerve-cell is purely nutritive.

The Function of the Axon.—The function of the axon is most conveniently studied in the spinal nerve trunks. These contain true axons, which arise from the multipolar cells in the grey matter of the spinal cord, as well as afferent fibres in connection with the cells of the ganglia of the posterior roots of the spinal nerves, the latter not being axons in the restricted sense of the term, but showing no difference in function from the axons proper except as regards the direction in which they normally conduct impulses.

The only function of these nerve fibres is to conduct impulses. During the propagation of an impulse an electrical current is produced in the fibre, and a current is also induced in it by injury. The excitability, conductivity, and electromotivity of the fibre are modified by the passage through it of a constant current. These phenomena have been already described in the chapter on Nerve, and need not be further alluded to in this connection.

It has already been pointed out that when an axon or other process is separated from the cyton to which it belongs, the severed part undergoes degeneration (fig. 7), usually described as Wallerian degeneration. This may be followed by a growth of fibres from the undegenerated portion into the distal part of a divided nerve trunk, the new growth being spoken of as regeneration.

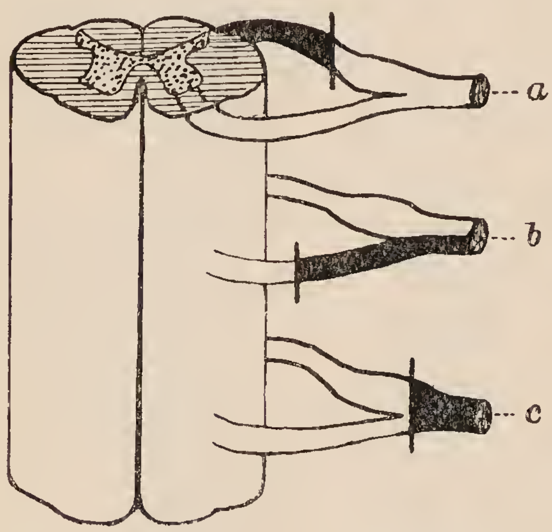


FIG. 7.—Diagram showing effects of section of spinal nerve roots.

Degenerated portions black. *b*, section of anterior root; *a*, section of posterior root central to ganglion; *c*, section of both roots peripheral to ganglion.

Degeneration and Regeneration of Nerves.—Most nerve fibres contained in a nerve trunk possess two sheaths, (1) a covering of lipoid material known as the myelin sheath, lying next to the fibre and interrupted at regular intervals, and (2) an outer, structureless covering, the neurolemma. Lying under the latter, about the middle of each myelin segment, is a nucleus surrounded by a little protoplasm.

When a nerve is divided the part which is cut off from the cell soon dies and undergoes degenerative changes. It shows a temporary rise in irritability followed by a gradual loss of excitability, and after two to five days the nerve is no longer excitable and will not conduct impulses.

The *degenerative changes* take place simultaneously along the entire length of the part of the nerve cut off from the cell, and are visible within twenty-four hours in a warm-blooded animal. The histological changes in a medullated nerve fibre consist first in a thickening of the neurolemma, with enlargement of the nuclei and increase of their surrounding protoplasm, so that the myelin sheath is broken into segments. A few days later the nuclei are seen to have multiplied and become more numerous; the myelin is in scattered droplets, and the axis cylinder is broken up into short lengths. The myelin and axis cylinder are gradually absorbed by the action of phagocytes, and after three or four weeks nothing is left but the neurolemma containing protoplasmic material in which are embedded many nuclei (fig. 8).

The chemical changes are equally marked. The complex lipoids which compose the myelin are broken down with the formation of simpler substances. Lecithin is split up into a nitrogenous base, choline, a fatty acid, which is usually oleic acid, phosphoric acid, and glycerol. In consequence of these chemical changes it is possible at

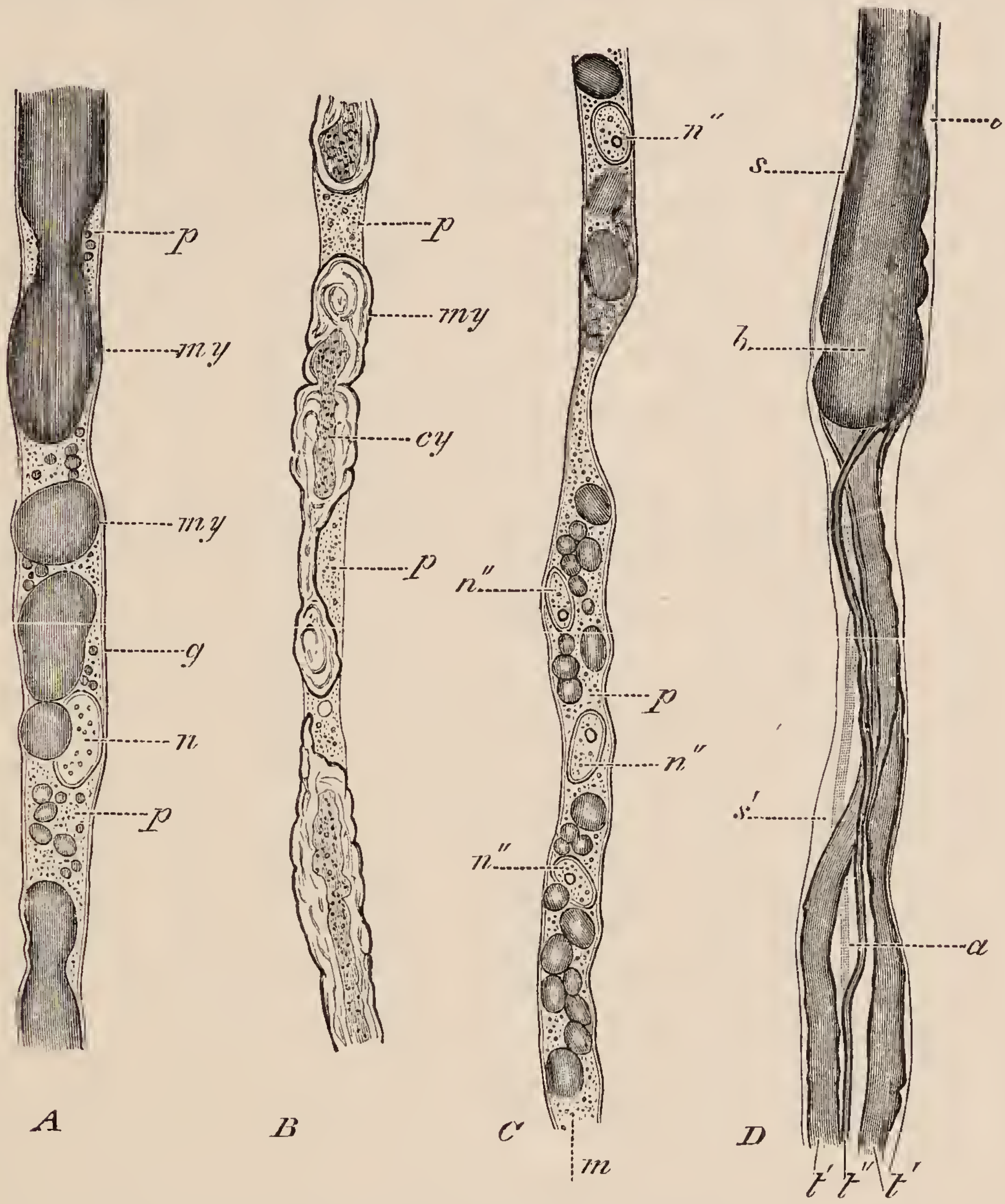


FIG. 8.—Degeneration and regeneration of nerve fibres in the rabbit. (Ranvier.) From Schäfer's *Essentials of Histology*.

A, part of a nerve fibre in which degeneration has commenced in consequence of the section, fifty hours previously, of the trunk of the nerve higher up ; *my*, medullary sheath becoming broken up into drops of myelin ; *p*, granular protoplasmic substance which is replacing the myelin ; *n*, nucleus ; *g*, neurolemma. *B*, another fibre in which degeneration is proceeding, the nerve having been cut four days previously ; *cy*, axis-cylinder partly broken up. *C*, more advanced stage of degeneration. *D*, commencing regeneration of a nerve-fibre. Several small fibres, *t′*, *t″*, have sprouted from the somewhat bulbous cut end, *b*, of the original fibre, *t* ; *a*, an axis-cylinder which has not yet acquired its medullary sheath ; *s*, *s′*, neurolemma of the original fibre.

this stage to distinguish degenerating from normal fibres by means of Marchi's fluid, which is a mixture of osmic acid with potassium bichromate. This fluid stains degenerating myelin black, but leaves normal nerve fibres unaffected. When all the myelin has been absorbed, the completely degenerated fibre no longer stains with Marchi's fluid; hence this method of identifying degenerating nerve

fibres is only available during the first three or four weeks after the fibres have been cut off from the nerve cells.

When the nerve fibres are completely degenerated, they can be distinguished from normal fibres by a special method of staining with hæmatoxylin called the Weigert-Pal method. The hæmatoxylin stains the myelin bluish black, and fibres from which the myelin has disappeared are left unstained.

When a nerve is divided the portion still connected with the cell does not degenerate, though changes take place in the nerve cell. Within one or two days the cell swells and the Nissl granules disappear; and after a time the cell shrinks. Later, regeneration usually occurs, and within three months the cell may return to a normal condition; in other cases complete atrophy of the cell takes place.

Regeneration.—After a time regeneration takes place and the nerve may be restored to a normal condition; this occurs more rapidly if the cut ends of a divided nerve are sutured together. Regeneration is brought about solely by the outgrowth of the part of the axon which is still in connection with the nerve cell, though the process is hastened by the presence of the neurolemma of the degenerated fibre, which seems to assist the outgrowth of the new fibre. The part played by the nerve cell is shown by the fact that extirpation of the nerve cells in a portion of the spinal cord prevents regeneration in motor fibres arising from that part of the spinal cord. Further, if the cut end of the peripheral portion of a divided nerve is covered by a rubber cap so as to prevent the growth of new fibres into it, no regeneration takes place.

Histological observations show that in the course of regeneration small fibrils with bulbous ends extend from the axis cylinders of the central portion of the divided nerve, and pass into the neurolemmal sheaths of the degenerated distal portion. The mode of growth seems to be similar to that which has been observed to occur in the embryonic nerve tissue of the frog. If fragments of the primitive nerve tube of a frog embryo are kept in lymph, the fibres can be seen under the microscope to grow out from the nerve cell.

It has been held by some observers that regeneration of the peripheral part of a divided nerve can occur apart from any outgrowth from the central end of the nerve, the process being called autogenetic regeneration. The experiments which have just been described show that this is not the case.

The time taken for a nerve to regenerate and to become functionally connected with the motor or sensory structures to which it was formerly attached varies with the distance to be traversed by the outgrowing fibres, and may be several months.

Regeneration still takes place if two nerves are divided and the central end of one is connected with the peripheral end of the other, provided that both nerves are either afferent or efferent. Thus, if the vagus nerve and the cervical sympathetic nerve are divided and the central portion of the vagus is sutured to the peripheral portion of the cervical sympathetic, regeneration will occur, and stimulation of the vagal portion of the united nerve will produce the effects formerly resulting from stimulation of the sympathetic nerve. This experiment shows that the effects of stimulation of a nerve are really due to changes in the nerve ending, and not to any specific change in the nerve itself.

When nerve fibres are divided in their course in the brain or spinal cord they undergo degeneration, but regeneration never occurs.

SECTION II.

THE SPINAL CORD (SPINAL MEDULLA).

The spinal cord consists of white matter (substance) and grey matter (substance), the former lying superficially, the latter deeply. The white matter is composed of medullated nerve fibres, running in a longitudinal direction, and having no neurolemma. The grey matter contains numerous nerve cells, arranged for the most part in two horns (columns), an anterior and a posterior, in each of which the cells form groups corresponding with the primitive segments of the body. Numerous fine medullated nerve fibres run into the grey matter, and terminate by forming arborisations in relation with the nerve cells. These fine fibres are called collaterals, and they arise at right angles from the medullated fibres of the white substance. The axons of each segmental group of cells in the anterior column of grey matter form an anterior root of a spinal nerve. The corresponding posterior nerve roots are formed of the axons of the cells in the respective spinal ganglia, and enter the spinal cord in the neighbourhood of the posterior horn (column) of grey matter. The course taken by these fibres in the spinal cord will be described later.

The spinal cord consists of two symmetrical halves, separated by the anterior median fissure in front and by a septum of pia mater called the posterior median fissure (septum) behind. The grey matter forms a crescent in each half in a transverse section, the convexity of each crescent being towards the middle line and being connected with the convexity of the crescent in the other half of the spinal cord by a commissure of grey matter. The central canal, containing cerebro-spinal fluid and lined by ciliated epithelium, lies in this commissure.

In front of the grey commissure, and uniting the white matter of the two halves of the spinal cord, is the white commissure.

The white matter is subdivided by the posterior horn of grey matter into an antero-lateral and posterior column (funiculus). The former is again roughly subdivided by the bundles which form the anterior nerve roots into an anterior and a lateral column.

THE REGIONS OF THE SPINAL CORD.

Three regions are distinguished in the spinal cord, the cervical, thoracic, and lumbar, each of which possesses definite structural characteristics. The cervical and lumbar regions exhibit enlargements corresponding with the outflow of nerves to the arm and leg respectively. The differences in structure between the three regions are best seen by a comparison of transverse sections. The cervical region is oval in section, the long axis of the oval lying transversely, its anterior median fissure is relatively shallow, and the central canal is in front of the true centre of the cord. The white matter is large in amount, the anterior horn (column) of grey matter is broad, and there is a well-marked septum subdividing the posterior column (funiculus) of white matter into medial and lateral portions. The dorsal region is cylindrical, its anterior median fissure is deeper, and the central canal is centrally placed. The anterior and posterior horns of grey matter are both narrow, and each grey crescent shows a projection in its concavity, known as the lateral horn. At the base of each posterior horn of grey matter, towards its medial aspect, is a special column of nerve cells, called Clarke's column (the dorsal nucleus). The lumbar region resembles the thoracic region in shape, depth of anterior median fissure, and position of central canal, but its white matter is absolutely and relatively smaller in amount, and both anterior and posterior horns of grey matter are broad in section. Generally speaking, the white matter diminishes progressively in amount from above downwards, and the grey matter is most abundant in the regions from which the outflow of the nerves to the limbs takes place.

THE NERVE CELLS OF THE SPINAL CORD.

The nerve cells in the grey matter are for the most part irregular in shape, but those in Clarke's column are somewhat fusiform, with their long axes in the long axis of the spinal cord. The cells in the anterior horn are larger in size than those in the posterior horn. The axons of the former emerge from the anterior surface of the spinal cord in several groups, which unite to form the anterior root of a spinal nerve. The axons of the cells of the posterior horn fall into two groups :

(1) those which run a short course in the grey matter and form terminal arborisations in relation with other nerve cells in the grey matter (cells of Golgi's second type), and (2) those which acquire a myelin sheath, run into the white matter, divide into a short descending and a longer ascending branch, and enter into the formation of the tracts of the white matter.

Certain well-defined groups of nerve cells may be recognised, three in the anterior horn, one in the lateral horn, the cells constituting Clarke's column, and those of the posterior horn. The anterior horn cells are very numerous in the cervical and lumbar regions, from which arise the nerves to the limbs.

The Nerve Roots.—The anterior and posterior roots meet a short distance from the lateral aspect of the spinal cord, and unite to form a spinal nerve. Just before it joins the anterior root the posterior root exhibits a swelling, the spinal ganglion; the unipolar cells of the ganglion are situated for the most part around the periphery of the structure, and the single process of each divides in a T-shaped manner into two fibres, one of which has a peripheral and the other a central direction.

The exit of the anterior root has already been described. The fibres of the posterior root, consisting of the central divisions of the processes of the ganglion cells, enter the spinal cord in the neighbourhood of the posterior horn of grey matter. Each divides into a short descending and a longer ascending branch. The longest ascending divisions run upwards in the posterior column to reach the medulla oblongata. The others turn into the grey matter at varying distances above their point of entry to terminate by arborisations around nerve cells. The descending fibres end in the same manner. Both ascending and descending fibres give off fine medullated collateral branches at intervals, these also entering the grey matter to form terminal arborisations in relation with nerve cells.

The Collateral Fibres. — Collaterals enter the grey matter from white fibres in all parts of the anterior, lateral, and posterior columns. Those from the long tracts of the white matter may be looked upon as associational in character, serving either to distribute the impulses conveyed by the main fibres and so to promote co-ordination, or to form part of a system of relays by which impulses are conveyed by short tracts from segment to segment of the spinal cord. The collaterals from, and terminations of, posterior root fibres, on the other hand, or many of them, are concerned with the formation of reflex arcs in the spinal cord itself; in addition to the fibres of the posterior root which have been described as running to the medulla oblongata in the posterior

column, there are four main groups of collaterals, including the terminations of main fibres, which run into the grey matter. These are (1) fibres to the anterior horn of the grey matter, (2) fibres to the posterior horn, (3) fibres to Clarke's column, and (4) fibres to the grey matter of the opposite half of the spinal cord, running across in the grey commissure. All these fibres end by forming arborisations in relation with nerve cells.

THE FUNCTIONS OF THE SPINAL CORD.

The functions of the spinal cord are two: (1) it is a centre or series of centres for reflex actions, and (2) it conducts impulses between the higher centres in the brain and the spinal nerves which transmit these impulses to or from the active or receptive tissues of the body. It is possible that the spinal cord may possess a low degree of automatic activity under certain conditions. Graham Brown has recently shown that in an animal from which the entire brain has been removed, and in which the afferent nerves from the limbs have been divided, there may occur under a certain degree of anæsthesia alternate flexion and extension of the limbs. No definite conclusions can, however, be based at present on this experiment.

SECTION III.

CONDUCTION IN THE SPINAL CORD.

The spinal cord forms a pathway for impulses which originate in the brain, and are distributed to all parts of the body through the anterior spinal nerve roots and the spinal nerves. It also conducts impulses which are set up by stimulation of afferent nerve endings, chiefly in the skin and muscles, and which reach it by the spinal nerves and posterior spinal nerve roots to pass in an upward direction to the brain.

There are two methods of conduction: (1) by long tracts of nerve fibres situated in the white matter, and (2) by short association tracts or relays. Most of the long tracts are found in the peripheral part of the white matter. The short tracts lie more deeply, their fibres running a little way in the white matter, then turning into the grey matter, to terminate by arborisations in relation with nerve cells, the axons of which in their turn form other short tracts in the white matter; so that impulses are conducted by a series of relays.

The tracts have been mapped out by two methods: (1) by observing the time during development at which the fibres in the various areas of the white matter of the spinal cord acquire a myelin sheath,

and (2) by studying the degeneration which follows various lesions, either pathological or experimentally produced.

The Myelination Method.—This method depends upon the fact that in the course of development the various conducting tracts acquire their myelin sheaths at different periods, so that by examining embryos at different stages of development it is possible to determine the limits of each particular tract. The longer fibres in the spinal cord become myelinated later than those fibres which run a shorter course; thus the pyramidal tracts do not acquire their myelin till after birth (fig. 9). The appearance of function coincides with the period of acquisition of myelin.

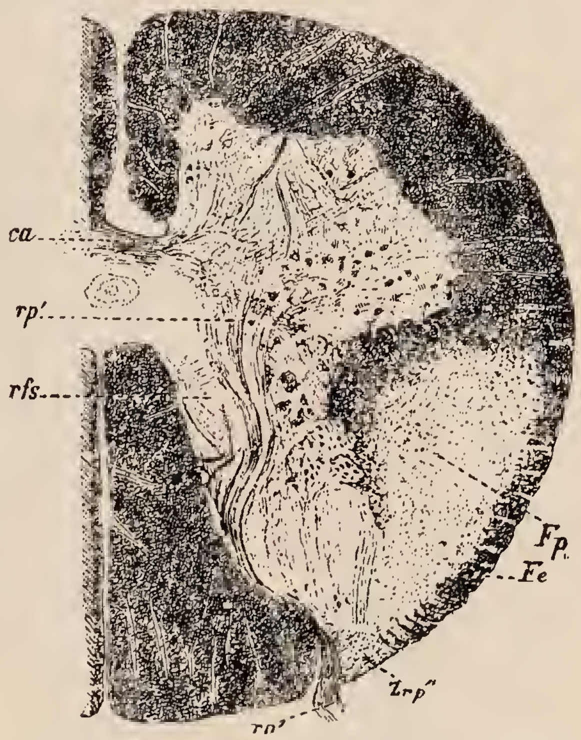


FIG. 9.—Section through the cervical spinal cord of a new-born child, stained by Weigert's method to show absence of medullation in pyramidal tract. (Bechterew. From Starling's *Principles of Physiology.*)

ca, anterior commissure; *Fp*, crossed pyramidal tract; *Fe*, direct cerebellar tract; *rp'*, posterior root fibres.

The Degeneration Method.—The degeneration method is based upon the fact that when a medullated nerve fibre is divided, the portion which is cut off from the nerve cell of which it forms a part undergoes degeneration. If the spinal cord is cut across in an animal, certain tracts degenerate in the part above the section, and other tracts degenerate in the part below the section. The former are said to have undergone ascending degeneration, and their fibres are axons of cells which lie below the point of section. The latter are said to have undergone descending degeneration, and their fibres are axons of cells which lie above the point of section. The extent of the degeneration varies in different parts of the white substance. In the case of the short tracts it extends for a limited distance from the section; in the case of the long tracts it may extend from the section to the upper or lower extremity of the spinal cord. From what has been said of the function of the neuron, it will be evident that the tracts which show descending degeneration are those which convey descending impulses, while those which show ascending degeneration are those which are concerned with conducting ascending impulses.

The chief conducting tracts of the spinal cord are shown in fig. 10.

THE DESCENDING TRACTS (OR FASCICULI).

The principal long descending tracts are the direct and crossed pyramidal tracts (the anterior and lateral cerebro-spinal fasciculi), both of which take origin in the cerebral hemisphere. The pre-central convolution on each side contains certain large pyramidal cells, known as Betz cells, the axons of which unite to form a tract which runs through

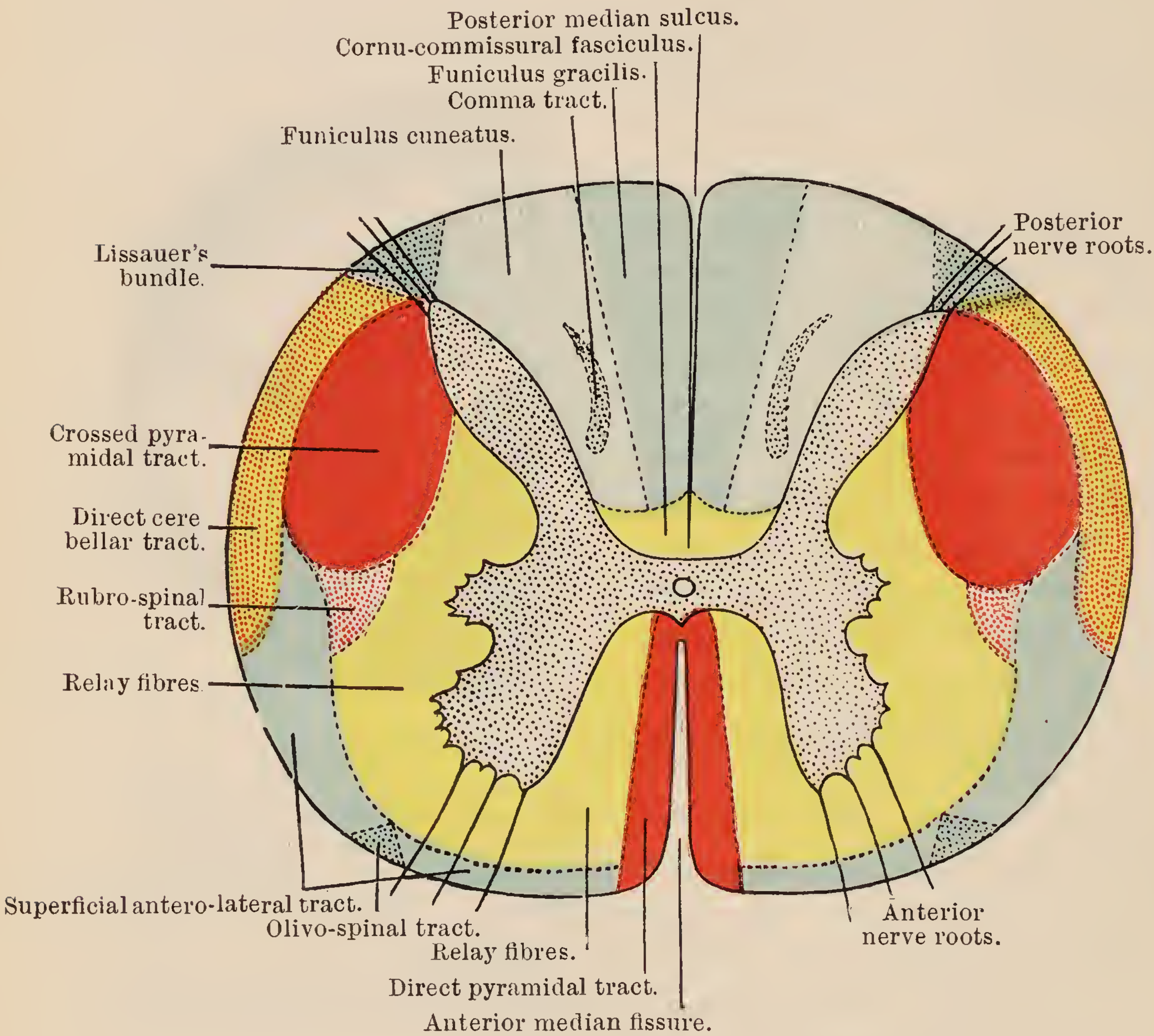


FIG. 10.—Diagram of the principal tracts in the spinal cord. (Gray's *Anatomy.*)

the mid-brain and pons to the medulla oblongata. In the latter structure the majority of the fibres in each tract cross to the opposite side to become the *crossed pyramidal tract* (lateral cerebro-spinal fasciculus) of the spinal cord, while the remaining fibres run down without crossing to become the *direct pyramidal tract* (anterior cerebro-spinal fasciculus) of the same side. Some of the uncrossed fibres, however, join the crossed pyramidal tract which has crossed from the opposite side.

The fibres of the crossed pyramidal tract terminate by running into

the grey matter at the base of the posterior horn of grey matter, where they form arborisations around nerve cells. By means of intermediate neurons these cells are brought into relationship with the cells of the anterior horn of grey matter, the axons of the latter forming the nerve fibres of the anterior nerve roots.

The fibres of the direct pyramidal tract cross in the spinal cord itself in the anterior white commissure to terminate in relation with the nerve cells of the grey matter of the opposite side.

Both pyramidal tracts convey motor impulses from one cerebral hemisphere to the opposite side of the body, a number of fibres terminating in each segment of the spinal cord, so that the tracts become progressively smaller as they descend. The fibres of the direct pyramidal tract all cross in the cervical and thoracic regions.

Less is known of the function of the other tracts and fibres which undergo descending degeneration. The best marked of these is the *rubro-spinal tract*, which lies in the lateral column, immediately in front of the crossed pyramidal tract, and consists of the axons of cells forming the red nucleus of the mid-brain. These fibres cross in the mid-brain close to their place of origin.

The *olivo-spinal tract* lies close to the surface opposite the anterior horn of the grey matter. As its name indicates, it is made up chiefly of fibres which are the axons of cells in the olivary nucleus of the medulla oblongata.

Vestibulo-spinal fibres, probably derived from the cells of Deiters' nucleus, are found in the antero-lateral column.

The *cerebello-spinal tract of Löwenthal*, also lying in the antero-lateral column, consists of scattered fibres derived from cells in the cerebellum.

The *comma tract*, lying in the posterior column, consists of the short descending branches of fibres which enter the spinal cord from the posterior nerve roots.

THE ASCENDING TRACTS.

The ascending tracts may be classified as exogenous or endogenous, according as they originate from cells in the ganglia of the posterior roots of the spinal nerves, or from cells in the grey matter of the spinal cord itself.

The exogenous tracts are the funiculus (fasciculus) gracilis (Goll's column), the funiculus (fasciculus) cuneatus (Burdach's column), and the bundle of Lissauer. The first and second of these together form the greater part of the posterior column, while the third lies close to the tip of the posterior horn of grey matter.

The *funiculus gracilis* occupies the mesial portion of the posterior

column. It consists of long ascending fibres derived from the posterior nerve roots; these terminate in the medulla oblongata by arborisation round the cells of the nucleus gracilis. The fibres of this tract are situated first in the funiculus cuneatus; as they ascend in the spinal cord they come to lie nearer the middle line and more posteriorly, so that in the cervical region those associated with the lower limb occupy a position mesial and dorsal to those which have entered the spinal cord at higher levels.

The fibres of the *funiculus cuneatus* are also ascending, and are derived from the posterior spinal nerve roots. Many of them terminate by arborisation in relation with the cells of the nucleus cuneatus of the medulla oblongata. Some, however, enter the grey matter of the spinal cord itself.

The *bundle of Lissauer* likewise consists of the ascending divisions of posterior root fibres. These have a short course and terminate by running into the grey matter of the spinal cord. Some authorities consider that certain fibres of the tract of Lissauer are intersegmental in character, because they acquire their myelin sheaths at a late stage, and also because they do not degenerate under conditions which lead to the degeneration of the other exogenous tracts, for example, in locomotor ataxia.

The chief endogenous ascending tracts are the direct cerebellar and the antero-lateral ascending tracts, which lie in the peripheral part of the antero-lateral column.

The *direct cerebellar tract* (dorsal spino-cerebellar fasciculus) consists of fibres which are the axons of cells in Clarke's column, and it is found only in the thoracic and cervical regions. It runs through the medulla oblongata and forms part of the restiform body, terminating finally in the vermis of the cerebellum.

The *antero-lateral ascending tract* (ventral spino-cerebellar fasciculus) is found in the lumbar as well as in the thoracic and cervical regions. Its fibres are derived from the cells of Clarke's column of the opposite side, and it runs through the medulla oblongata and pons to the mid-brain, where it turns round to form part of the superior cerebellar peduncle, and ends in the vermis of the cerebellum.

Associated with the ventral spino-cerebellar tract are two other groups of fibres: (1) the *spino-thalamic*, which ascend through the medulla oblongata, pons, and mid-brain to terminate in the thalamus, and (2) the *spino-tectal*, which terminate in the corpora quadrigemina. The ventral spino-cerebellar, spino-thalamic, and spino-tectal fasciculi together form what was formerly known as Gowers' tract.

THE PHYSIOLOGICAL PATHS IN THE SPINAL CORD.

Division of the posterior spinal nerve roots of the nerves supplying a limb results in the immediate loss of all sensation in the limb. There is also loss of muscle tone, and the limb is paralysed owing to the absence of afferent impressions from it. Later, the afferent fibres undergo degeneration centrally to the lesion, if the latter is between the root ganglion and the spinal cord.

Complete section of the spinal cord in the lower thoracic region is followed by immediate loss of movement and sensation in the hind limbs. There is also loss of vascular tone with passive dilatation of the blood-vessels (passing off in twenty-four hours), and the hind limbs become poikilothermic, that is, their temperature varies with that of the surrounding medium. Further, the reflex visceral centres in the lumbar region are cut off from the inhibitory impulses from the higher centres, so that micturition and defæcation become simple reflexes. Later, the motor fibres below the point of section and the afferent fibres above the section, which have entered by posterior roots below the lesion, undergo degeneration.

Hemisection of the spinal cord in the lower thoracic region results in motor paralysis of the homolateral hind limb, accompanied by loss of muscle sense and tactile discrimination on the same side. There is also loss of tactile localisation, and of the senses of heat, cold, and pain in the contralateral hind limb, the fibres for these senses having crossed in the spinal cord shortly after their entrance by the posterior roots. Immediately below the lesion, however, this sensory paralysis occurs in a narrow zone on the side of the section, depending on fibres which have been divided before their crossing. The remote effects of hemisection consist in ascending and descending degeneration of the divided fibres above and below the lesion respectively.

Transection at various levels shows that the *motor paths* and the paths for *muscle sense* and for *tactile discrimination* cross the middle line above the level of the spinal cord, whereas the paths for *tactile localisation*, the senses of heat and cold, and the sense of pain cross in the spinal cord itself in the vicinity of the posterior roots conveying these impulses from the periphery. Further, in the disease known as syringomyelia, in which the central canal of the spinal cord is dilated and there is pressure on the adjacent structures and interference with their functions, it is found that the sense of pain may be lost while those of temperature and tactile localisation are unimpaired, or the temperature sense may be lost while the other two senses are intact. There are, therefore, separate bundles of fibres for the transmission of the different impulses which give rise to these various sensations.

In man, the motor impulses are conveyed from the brain to the neurons of the different anterior nerve roots almost entirely by the pyramidal (cerebro-spinal) tracts, but in the lower animals other tracts are also used. As has already been stated, the greater part of the motor path from the brain crosses in the medulla oblongata to form the crossed pyramidal tract, and the fibres of this tract terminate in the grey matter of the spinal cord in relation with the neurons connected with the anterior nerve roots of the same side. Hence a lesion involving one of these tracts results in motor paralysis on the same side of the body. There will be a certain degree of weakness of muscles on the opposite side of the body after a unilateral lesion of the human spinal cord, because of the interference with the direct pyramidal tract, the fibres of which cross immediately before their termination; but this is relatively insignificant, and, as the fibres of the direct pyramidal tract have all crossed in the cervical and thoracic regions, a unilateral lesion in the lower thoracic region will result in motor paralysis of the homolateral hind limb only.

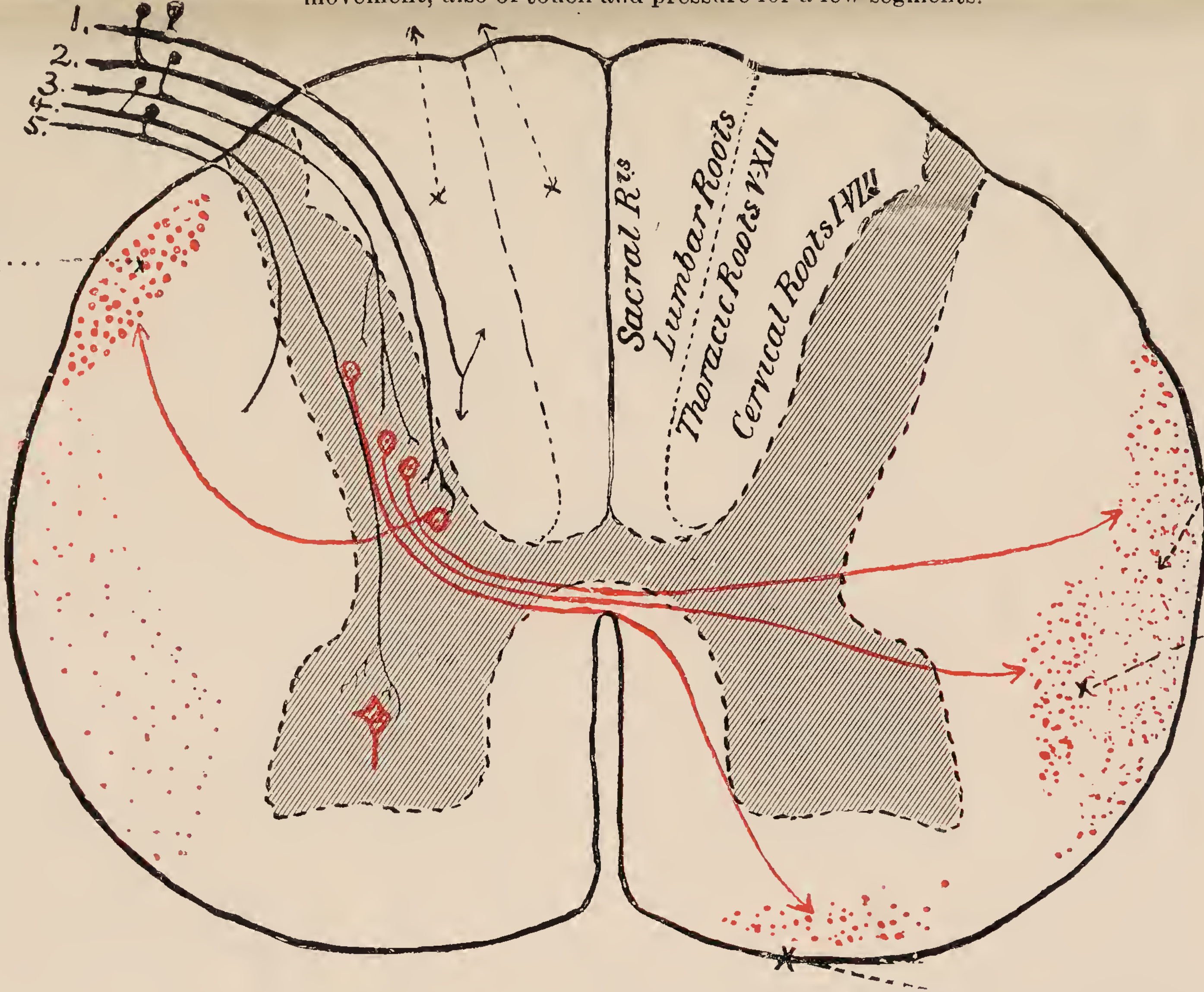
The localisation of the paths for the various sensory impulses (fig. 11) has been ascertained by the study of diseased conditions in man, as well as by observing the results of experimental localised lesions in animals. By such methods it has been shown that the funiculus gracilis and the funiculus cuneatus are concerned with the transmission of those kinæsthetic (muscle sense) impulses which pass to the cerebral hemispheres and cerebellum, the paths crossing in the medulla oblongata just above the decussation of the motor tracts; a cell station occurs on these paths below their decussation.

The direct cerebellar and the antero-lateral ascending (Gowers') tracts also convey kinæsthetic impulses, but these differ from those conveyed to the cerebral hemispheres in that they are not connected with conscious sensation. Both these tracts are uncrossed in their course to the cerebellum, and in neither is there a cell station on the path.

The fact that the four long ascending tracts convey impulses of muscle sense is to be associated with the importance of the function of equilibration, a function which requires for its performance delicate muscular adjustments.

Impulses of pain, heat, and cold are conveyed into the posterior horn of grey matter by fibres of the posterior roots. They then pass by a second neuron to the spino-thalamic fibres of the opposite side, and thus reach a cell station in the optic thalamus, from which they are passed on to the cerebral cortex. Tactile impulses pass up the posterior column of the same side for four or five segments before

movement, also of touch and pressure for a few segments.



6. Homolateral unconscious impulses underlying co-ordination and reflex muscular tone.

7. Heterolateral unconscious afferent impulses underlying muscular co-ordination and reflex tone.

8. All impulses of pain, of heat and of cold (heterolateral).

9. Heterolateral impulses of touch and pressure.

Fig. 11.—Diagram to illustrate the termination of peripheral afferent fibres in the spinal cord, and the origin of the secondary central paths, with a brief summary of their function. (W. Page May.) From Starling's *Principles of Physiology*.

1, bundles of fibres passing up in the posterior column, many to spinal cord, the remainder to nuclei in medulla oblongata; 2, fibres terminating round cells in Clarke's column; 3, fibres arborising round cells in posterior horn; 4, fibres arborising round anterior horn cells; 5, fibres to lateral column; 6, direct cerebellar tract; 7 and 8, Gowers' tract; 8, spino-thalamic and spino-tectal tracts; 9, ascending tract in anterior column.

forming a cell station in the grey matter, and being conveyed by other neurons to the anterior column of the opposite side. They also ultimately reach the optic thalamus, and pass to the cerebral cortex by a fresh relay (fig. 28).

SECTION IV.

REFLEX ACTION.

In the course of evolution survival has depended, to a large extent, upon the rapidity and efficiency with which reflex movements are carried out; and the essential characters of a reflex action are (1) that it should be rapid, and (2) that it should be co-ordinate, that is, that the muscles concerned in the reflex act should contract together so as best to attain the end for which the reflex exists. Further, the response to a stimulus must be limited in its extent, and must not involve the whole muscular system. Finally, evolution is made possible by the capacity of the central nervous system to form new reflexes, and this capacity is the basis of habit and of educability. It is in this respect that the nervous system of man has become so much more highly differentiated and complex than that of the lower animals.

In man the reflex functions of the spinal cord have become to a large extent subordinate to those of the brain; and the spinal cord, when separated from the brain as a result of injury, displays a comparatively feeble reflex power. In the lower animals the spinal reflexes are more pronounced, and can be readily studied either in the pithed frog or in a spinal mammal, *i.e.* an animal which is allowed to recover after transection of the spinal cord, this being usually made in the upper thoracic region.

The Reflex Arc.—When a stimulus falls upon a sensory surface or sense organ, which is called a receptor, it gives rise to an impulse which is conveyed by an afferent nerve to the spinal cord. Here it travels through a number of neurons, where its character is modified, and finally the impulse leaves the spinal cord along an efferent nerve to reach the muscle or gland which responds to the stimulus. This path is called a reflex arc, and consists of (1) a receptor, (2) afferent nerve, (3) neurons in the spinal cord, (4) efferent nerve, and (5) muscle or gland (fig. 12).

Interruption of the arc at any point abolishes the reflex action.

The time occupied by an impulse in travelling from the receptor through the central nervous system to the muscle or gland (effector organ) is called the *total reflex time.* A part of this time is occupied in the transmission of the impulse along the afferent and efferent

nerves and by the latent period of the effector organ. When this is deducted from the total reflex time, a period remains, known as *reduced reflex time*, which is occupied by the passage of the impulse through the neurons in the central nervous system. Its duration varies with the complexity of the reflex action, and is taken up mainly in the passage of the impulse across the synapse between the axon of one neuron and the dendrites of the next neuron, the synapse offering a certain resistance to this passage.

It has been found in the frog, for example, that when one leg moves in response to a stimulus applied to that leg, the reduced reflex time is rather less than one-hundredth of a second. The reduced reflex time

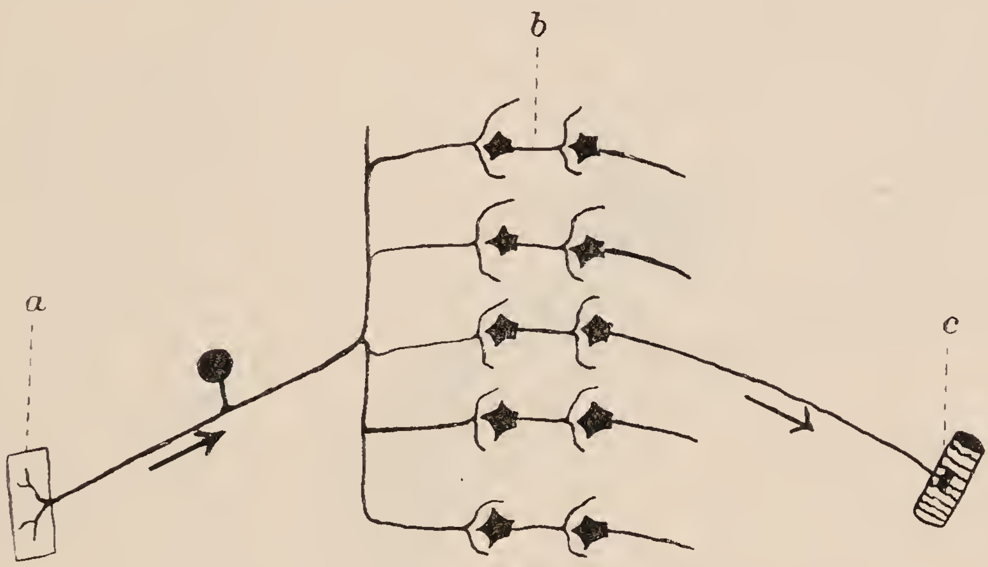


FIG. 12.—Diagram of a reflex arc.
a, receptor ; *b*, intermediate neuron ; *c*, muscle fibre.

for reflex winking of the eye in man has been estimated at about one-twentieth of a second.

The time required for the production of a reflex becomes less with increasing strength of the stimulus, and becomes longer when the spinal cord is fatigued or is under the influence of drugs, such as chloroform. Increase in the strength of the stimulus may also increase the extent of the reflex response. If the strength of stimulus necessary to elicit a particular reflex is determined, and the experiment is repeated with a stronger stimulus, there may be (1) an increase in the strength of the original response, and (2) additional muscles may also be thrown into contraction. In other words, with a stronger stimulus there is a spread of the excitation in the grey matter of the spinal cord, whereby additional reflex arcs become involved ; this spreading of the excitation is known as *irradiation*.

When, for example, a harmful (nociceptive) stimulus, such as a sharp prick, is applied to the sole of the foot in the spinal dog, the leg is flexed and withdrawn from the stimulus. When the strength of

the stimulus is increased, the muscular response may extend to the opposite leg and to other parts of the body. This experiment shows that an impulse reaching the spinal cord finds its way most easily along a certain path, and that its spread up or down the cord is normally prevented by the resistance offered by neighbouring synapses.

After the injection of strychnine this resistance disappears, and an impulse reaching the cord at any level evokes generalised muscular movements which are inco-ordinate. The normal limitation of the reflex response is thus an important part of the means by which the object of the reflex is obtained.

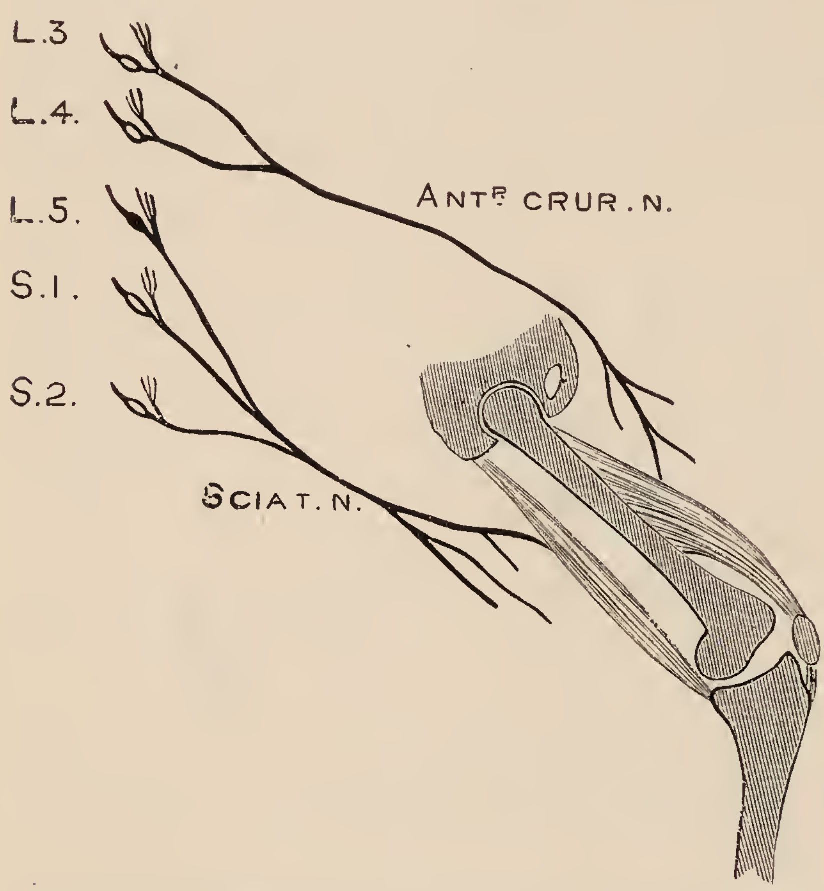


FIG. 13.—Diagram to show muscles and nerves concerned in Sherrington's experiment on the reciprocal innervation of antagonistic muscles. (Starling's *Principles of Physiology.*)

L.3, L.4, L.5, 3rd, 4th, and 5th lumbar nerve roots. S.1, S.2: 1st and 2nd sacral roots.

Inhibition. — Reflexes may be restrained or completely inhibited by impulses, voluntary or involuntary, from the higher nerve centres. If a reflex is elicited in a frog from which the cerebral hemispheres have been removed, and then a crystal of common salt is applied to the optic lobes and the stimulus is repeated, the reflex movement may not occur, owing to inhibitory impulses resulting from the stimulation caused by the salt. A reflex act, which is in progress, may also be checked or inhibited by the advent of another stimulus to the central nervous system. Further, inhibition forms a constituent of many reflex actions, the movement of certain muscles being accompanied by the simultaneous inhibition of others.

Reciprocal Innervation.—When firm pressure is applied to the sole of the foot in a spinal dog, it responds by rapid extension of the leg, due partly to contraction of the extensor muscles of the thigh. It is evident that this extension is only possible if the flexor muscles (hamstrings) are at the same time relaxed, and their relaxation is not a passive but an active process and forms an essential part of the extensor reflex. This can be shown by separating the extensor and flexor

muscles of the thigh from their lower attachments and connecting them with recording levers. It is then found that the application of firm pressure to the foot produces simultaneously contraction of the extensor and inhibition of the flexor muscles.

This process, which holds good for the action of antagonistic muscles in general, is spoken of as reciprocal innervation; and its importance for the efficiency of a reflex action is demonstrated by the effects which are observed when it no longer takes place. The scratch reflex, for example, in the dog consists of rhythmic movements of flexion and extension of the leg, each flexion recurring about four times a second; in the normal animal the movements are directed to the removal of an irritant. The same reflex can be evoked in a spinal dog by the application of a weak electrical stimulus to the skin of the "scratch area," which occupies the thoracic region; with each flexion of the thigh the flexor muscles contract and the extensors are inhibited; with each extension of the thigh the converse takes place. After the injection of strychnine into the animal, the application of the stimulus produces contraction of both flexor and extensor muscles, and, since the extensors are the more powerful, the limb becomes rigidly extended and the reflex can no longer be carried out.

Since the muscles in the body are limited in number, whereas the impulses which may reach the spinal cord or brain are almost infinite in variety, it is clear that the same muscle must at times be used in response to different kinds of stimuli. For example, the flexor muscles of the leg contract during the scratch reflex, and also in response to a painful stimulus; in each case the impulse travels down the efferent nerve to the muscle. The motor side of the reflex arc is, therefore, to some extent identical for both the scratch reflex and the response to the painful stimulus; it is therefore spoken of as a *final common path*.

Further, we find, as might be expected, that the final common path can only be traversed by one set of impulses at the same time. If, for example, the scratch reflex is evoked in a spinal animal, and while it is taking place a strong nociceptive stimulus is applied to the sole of the foot, the scratch reflex immediately stops and is replaced by flexion of the leg (fig. 14). Conversely, if the flexion reflex is in progress, the application of the scratch stimulus, if sufficiently strong, may inhibit the flexion reflex and produce the scratch reflex.

The two reflexes cannot co-exist; one or the other must prevail, and the one which prevails (prepotent reflex) is usually that which is most important for the well-being of the body. The fact that two opposed reflexes such as those just mentioned cannot co-exist is of

great importance, since, if they were taking place simultaneously, neither would be carried out effectively.

Facilitation.—When a stimulus which is insufficient to produce a reflex response is repeated at short intervals, the reflex is often ultimately evoked (fig. 15). Evidently the preceding stimuli, though causing no visible response, bring about some change in the neurons of the reflex arc whereby the stimulus finally becomes effective. This process is known as facilitation, and forms the basis of habit. Each time a reflex action takes place it becomes easier for it to be brought about on a subsequent occasion. This is well seen in the case of many skilled movements, which, in the first instance, are learnt by voluntary effort; in time the adjustment of the impulses concerned in the carrying out of these movements becomes so exact that, in response to a suitable stimulus, they take place without voluntary effort and almost independently of consciousness.

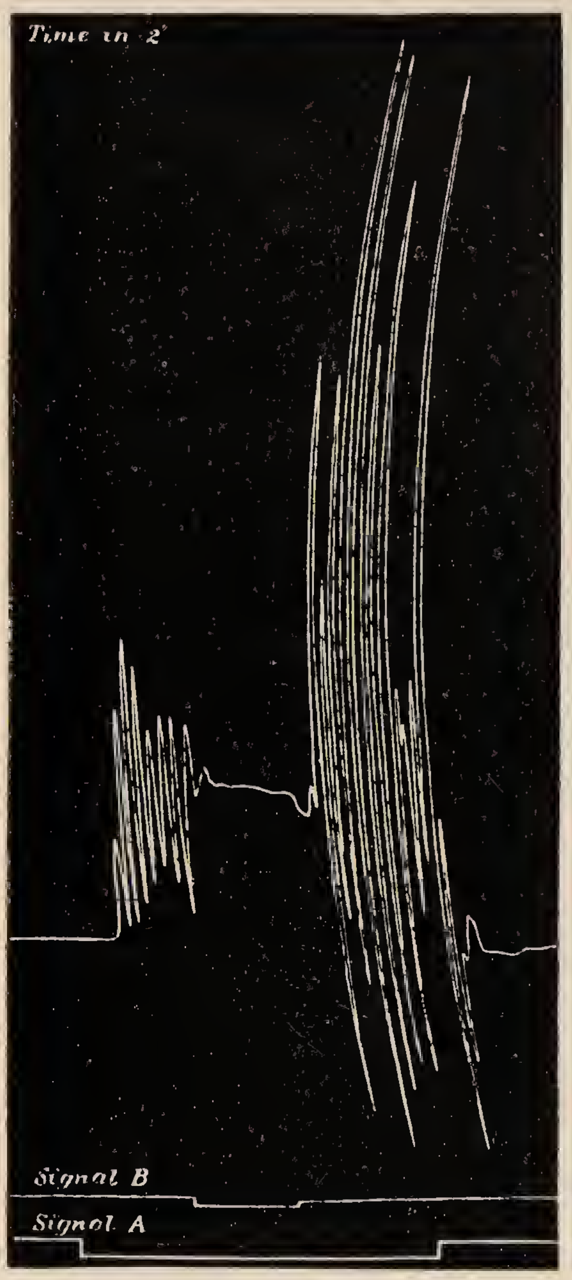


FIG. 14.—Scratch reflex temporarily inhibited by application of a painful stimulus to foot. (Starling's *Principles of Physiology.*)

Signal A, stimulation of scratch area. Signal B, stimulation of paw by strong induction shock.

By these means reflex actions are so adjusted as to bring about a definite movement as rapidly as possible in response to a suitable stimulus. For this purpose the co-existence of consciousness is not necessary, indeed it is sometimes a hindrance. Many reflexes, particularly those occurring in connection with the visceral system, take place without affecting consciousness at all. Other reflexes, for instance the closing of the eye when an object approaches it suddenly, are associated with consciousness, though the reflex act precedes and takes place independently of consciousness. A third group of reflexes, for example micturition, can to some extent be modified by voluntary impulses.

The Knee Jerk.—Reflex action may be brought about not only by stimuli falling upon the surface of the body, but by stimuli arising within the body itself, for instance in the joints and muscles. Reflexes

which are brought about by impulses originating in the deeper tissues of the body are often called "deep" reflexes. One of the most important is the knee jerk, which consists in contraction of the extensor

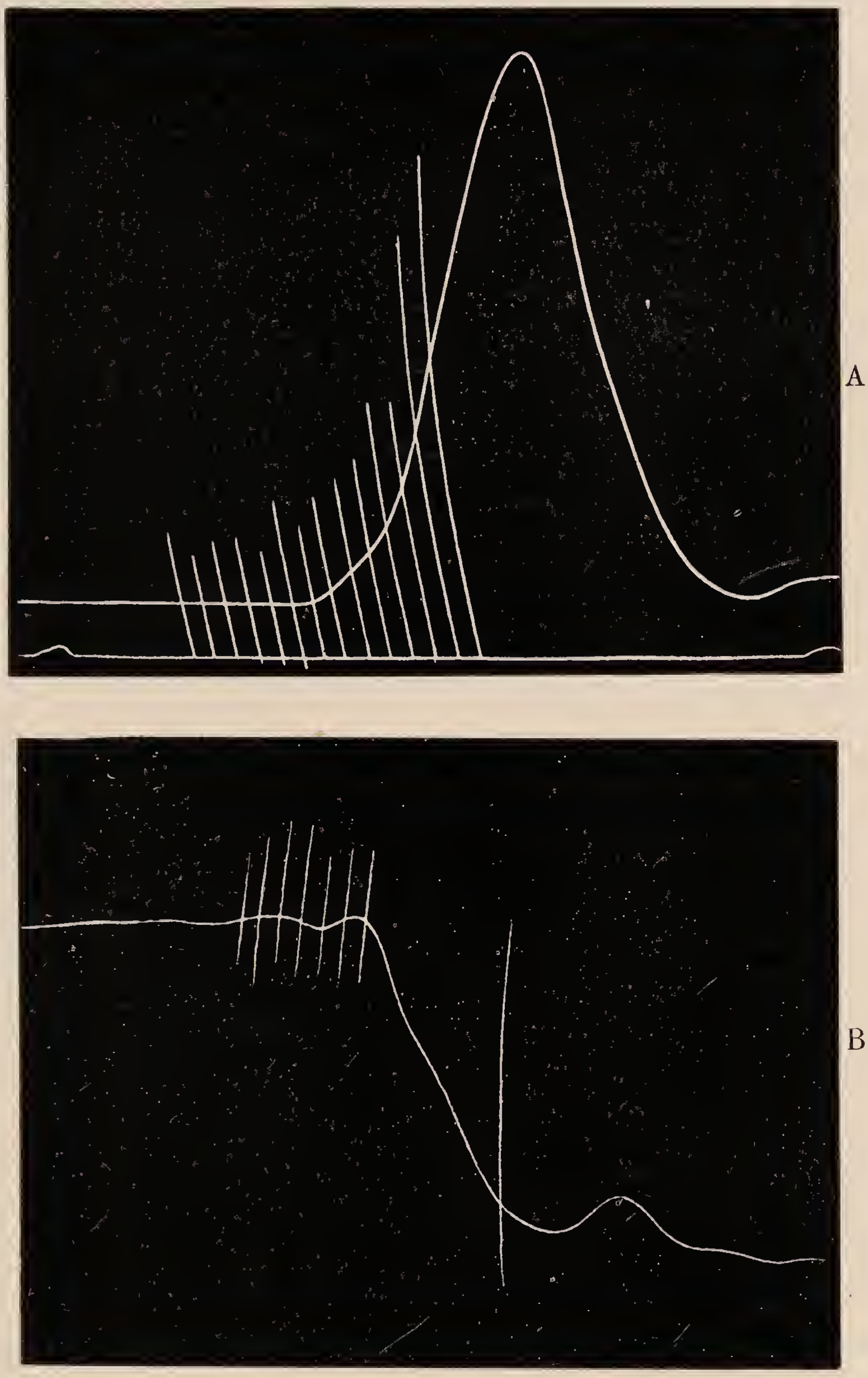


FIG. 15.—Reflexes produced by summation of weak stimuli. (Sherrington. Starling's *Principles of Physiology.*)

A, Reflex contraction of flexor muscles of knee. B, Reflex inhibition of extensor muscle. In each case the effect follows the sixth stimulus, the stimuli being applied to the central end of the internal saphenous nerve.

muscles of the thigh in response to a sharp tap on the patellar tendon. The stretching of the extensor muscles by this tap gives rise to a stimulus in sensory structures (muscle-spindles) within the muscle itself; from these structures the impulse passes to the spinal cord along the afferent nerve fibres of the muscle.

The reflex character of the knee jerk has been denied on the ground that it is a single twitch, whereas in genuine reflexes there is a rhythmic discharge of impulses to the muscle. This argument is discounted by the fact that the sudden extension of the leg which is produced by applying pressure to the foot of a spinal animal is undoubtedly a reflex action and is also a single twitch.

The knee jerk takes place very rapidly, the reduced reflex time being only 0·002 second; and though it must be regarded as a true reflex, the impulse passes, in all probability, through only one synapse in the spinal cord.

In man the part of the spinal cord concerned with the knee jerk is the third and fourth lumbar segments; and the knee jerk is abolished either by destruction of this part of the spinal cord or by division of the afferent or efferent nerves of the extensor muscles of the thigh. The knee jerk is absent in locomotor ataxia, in which the posterior lumbar nerve roots are diseased and the afferent path of the reflex arc is interrupted. Exaggeration of the knee jerk may be brought about by section of the hamstring muscles or of the afferent nerves from these muscles.

The knee jerk can also be increased by impulses from the higher parts of the central nervous system. If, for example, the fists are firmly clenched at the moment at which the knee jerk is elicited, the jerk is more marked, this being called *reinforcement* of the knee jerk. Further, it is often exaggerated in disease of the cerebral cortex or of the pyramidal tracts, probably owing to the cutting off of restraining impulses which normally pass to the spinal cord from the brain.

The knee jerk and other similar reflexes serve to protect joints and ligaments from injury when a sudden strain occurs, which tends to separate the joint surfaces or to stretch ligaments; and the extreme rapidity of the reflex is no doubt associated with this protective function.

The production of the knee jerk and other tendon reflexes is dependent on the existence of *muscle tone*. The skeletal muscles are in a constant condition of slight tonic contraction, which is due to the continuous discharge of impulses from the spinal cord to the muscles, as is shown by the following observation. When the brain of a frog is pithed and the animal is suspended by its head, the muscles do not become flaccid and the limbs remain very slightly flexed. When the spinal cord is destroyed, or the posterior roots of the spinal nerves are divided, the limbs become fully extended and the muscles lose their tone.

In mammals, muscular tone is lost when the skeletal muscles are cut off from the central nervous system, or during deep anæsthesia.

The normal maintenance of this tone is really a reflex action and is dependent on afferent impulses, which in the mammal originate chiefly in the muscles themselves. It is abolished, therefore, not only by section of motor nerves, but also by section of the posterior nerve roots containing the afferent fibres coming from the muscles. Impulses passing down the spinal cord from the brain may also control and modify muscular tone; and this is sometimes greatly increased, when the passage of these impulses is prevented by injury to the spinal cord in animals, or by disease of the pyramidal tract in man.

The afferent impulses passing from muscles to the spinal cord may not only bring about reflex actions, but play an important part in the co-ordination of reflex actions brought about by external stimuli. If the afferent nerves from the muscles of a limb are divided, the movements of that limb are inco-ordinate (ataxic), even though cutaneous sensation is not interfered with. On the contrary, division of the cutaneous nerves has but little effect upon the co-ordination of muscular movements, provided the afferent muscular fibres are intact. For instance, a cat, even after the division of all the cutaneous nerves to its four paws, is still able to balance itself almost as accurately as a normal animal.

The Visceral Spinal Reflexes.—Local centres exist in the spinal cord associated with reflexes connected with the blood-vessels and sweat glands.

Centres also exist in the lumbo-sacral region of the spinal cord for the functions of micturition, defæcation, erection, and parturition. All these centres are normally controlled to a greater or less degree by the higher centres, but the reflex function of each can be carried out when all connection with the higher centres has been severed.

SPINAL SHOCK.

This is a condition, following transverse section of the spinal cord, in which the reflex functions of the cord are abolished in the part posterior to the lesion. It is seen in its simplest form in the frog. If the spinal cord of a frog is divided just posterior to the medulla, the muscles of the limbs become flaccid and remain in this condition for about half an hour. During that time no reflex can be elicited in the limbs. As the shock passes off, muscular tone returns, the animal assumes a fairly normal position, and reflex muscular contractions can once more be evoked. In mammals the condition of spinal shock is more prolonged. Section of the spinal cord below the origin of the phrenic nerves results in loss of muscle tone and of vascular tone in the body posterior to the lesion. The sphincters of the anus and bladder are relaxed, the reflexes for defæcation and micturition are abolished, and muscular reflexes cannot be elicited.

The condition lasts for a few days, at the end of which time the blood-vessels and muscles have regained their tone, the sphincters of the anus and bladder are contracted, defæcation and micturition occur reflexly, and it is possible to evoke muscular reflexes.

The condition of spinal shock is not due to the effect of the operation, nor to the fall of blood pressure, for it only affects the region of the cord posterior to the lesion. It is believed to result from the cutting off of impulses which are continually reaching the cord from the higher centres.

SECTION V.

THE BRAIN.

There are three main divisions of the brain, named respectively the fore-brain, mid-brain, and hind-brain. The fore-brain consists of the cerebral hemispheres and most of the structures bounding the third ventricle, the mid-brain of the corpora quadrigemina and the cerebral peduncles, and the hind-brain of the cerebellum, pons, and medulla oblongata.

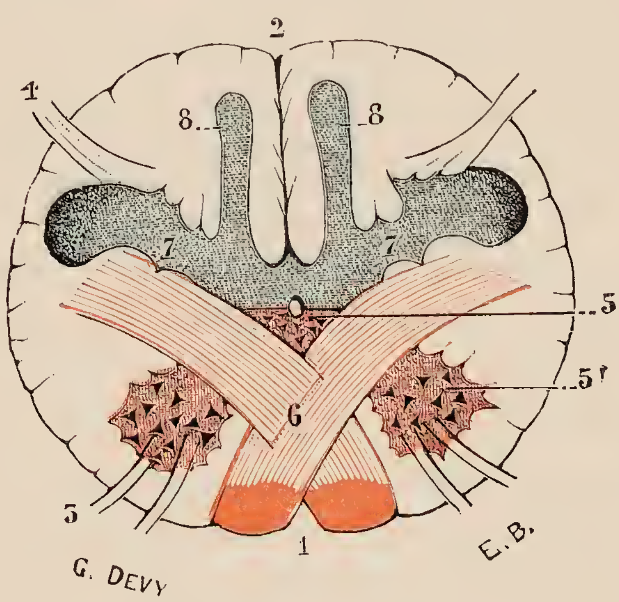


Fig. 16.—Section of the medulla oblongata at the level of the decussation of the pyramids. (Testut.) From Gray's *Anatomy*.

1, Anterior median fissure; 2, posterior median sulcus; 3, motor roots; 4, sensory roots; 5, base of the anterior horn, from which the head (5′) has been detached by the crossed pyramidal tract; 6, decussation of the pyramids; 7, posterior horns (in blue); 8, gracile nucleus.

THE MEDULLA OBLONGATA.

The medulla oblongata may be regarded structurally as an upward continuation of the spinal cord, in which certain conducting tracts decussate, and the structure of which is further complicated by the appearance of cell stations on some of these tracts. Owing to the decussations and also to other modifications, the upper part of the medulla oblongata differs greatly in structure from the lower part. In the upper part, the pyramidal tracts occupy a position anteriorly close to the anterior median fissure, each on the side of the cerebral hemisphere from which it is derived. The tracts are here known as the pyramids. In the lower part of the medulla oblongata, the greater part of each pyramid crosses to take up the position which it occupies in the spinal cord as the crossed pyramidal tract (fig. 16). The decussating fibres separate the grey matter continuous with the anterior horn of the spinal cord into two parts. One, continuous with the head of the

horn, is pushed towards the lateral aspect of the medulla, and is continued upwards as the nucleus ambiguus, which is the nucleus of origin of the cerebral fibres of the spinal accessory nerve and of the motor fibres of the vagus, glossopharyngeal, facial, and trigeminal nerves. The portion of grey matter which is continuous with the base of the anterior horn lies behind the decussating pyramids, and in the upper part of the medulla oblongata lies close to the floor of the fourth ventricle, where it forms the nuclei of the hypoglossal nerves. The further upward continuation of this part forms the nuclei of the sixth, fourth, and third nerves in the mid-brain.

The grey matter which is continuous with the posterior horn of the spinal cord lies nearly transversely in a section of the lower part of the medulla oblongata, and two outgrowths appear on its dorsal aspect, one projecting into the funiculus gracilis, the other into the funiculus cuneatus. These outgrowths form the *nucleus gracilis* and the *nucleus cuneatus* respectively, and in them the fibres of the corresponding funiculi terminate by arborisation. Most of the axons of the cells of the two nuclei pass forward, and cross the middle line as internal arcuate fibres to form the lemniscus or fillet of the opposite side. This decussation takes place just above that of the pyramids (fig. 17). The fillet runs upwards dorsal to the pyramid to terminate in a cell station in the thalamus. It is joined in the medulla oblongata by the spino-thalamic fibres, which have already decussated in the spinal cord.

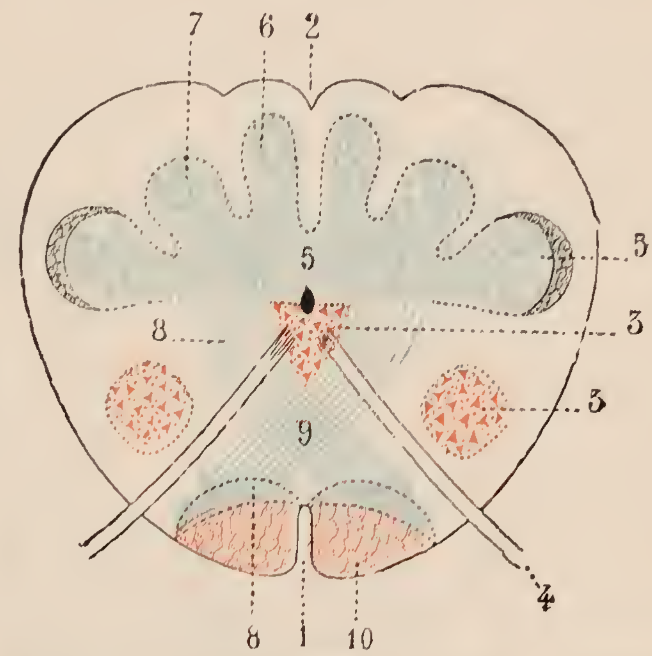


FIG. 17. — Transverse section passing through the sensory decussation. (Schematic.) (Testut.) From Gray's *Anatomy*.

1, Anterior median fissure; 2, posterior median sulcus; 3, 3', head and base of anterior horn (in red); 4, hypoglossal nerve; 5, bases of posterior columns; 6, gracile nucleus; 7, cuneate nucleus; 8, 8, lemniscus; 9, sensory decussation; 10, pyramid.

The sensory decussation separates the base from the apex of the posterior horn of grey matter. The base forms a column of grey matter in which are found the sensory nuclei of the vagus and glossopharyngeal nerves, and which is connected with the nuclei of the vestibular nerve and of the sensory root of the facial nerve. The head forms the spinal nucleus of the fifth nerve.

The upper portion of the medulla oblongata is characterised mainly (1) by the fact that the central canal comes to the surface posteriorly

and opens out into the fourth ventricle, and (2) by the appearance of a lateral projection behind the pyramid, known as the olive, and containing a folded sheet of grey substance internally, the olivary nucleus. In the floor of the fourth ventricle are the nuclei of the hypoglossal and of the vagus and glossopharyngeal nerves. Lateral to these nuclei are the nucleus gracilis and nucleus cuneatus. Near the nucleus cuneatus is the spinal (descending) root of the fifth nerve, and ventral to the hypoglossal nucleus is the *nucleus ambiguus*. The interior of this part of the medulla oblongata is occupied chiefly by the olivary nucleus and the *formatio reticularis*. The latter consists of nerve fibres, some running transversely and some, including those of the fillet, running longitudinally. It also contains some scattered nerve cells. Ventral to the formatio reticularis is the pyramid, and lateral to the nucleus cuneatus and the spinal root of the fifth nerve is a tract of nerve fibres, the restiform body or inferior peduncle of the cerebellum. The hypoglossal nerve crosses the formatio reticularis from its nucleus to emerge in front of the olive, and the vagus and, at a higher level, the glossopharyngeal nerve take a more lateral course through the formatio reticularis to reach the surface behind the olive. Some of the internal arcuate fibres, arising from nerve cells in the nucleus gracilis, nucleus cuneatus, and olivary nucleus, cross the middle line to form part of the restiform body. The external arcuate fibres are derived from the gracile and cuneate nuclei and pass forward to the anterior median fissure, where they sweep backward over the pyramid and olive of the opposite side to join the restiform body (fig. 18).

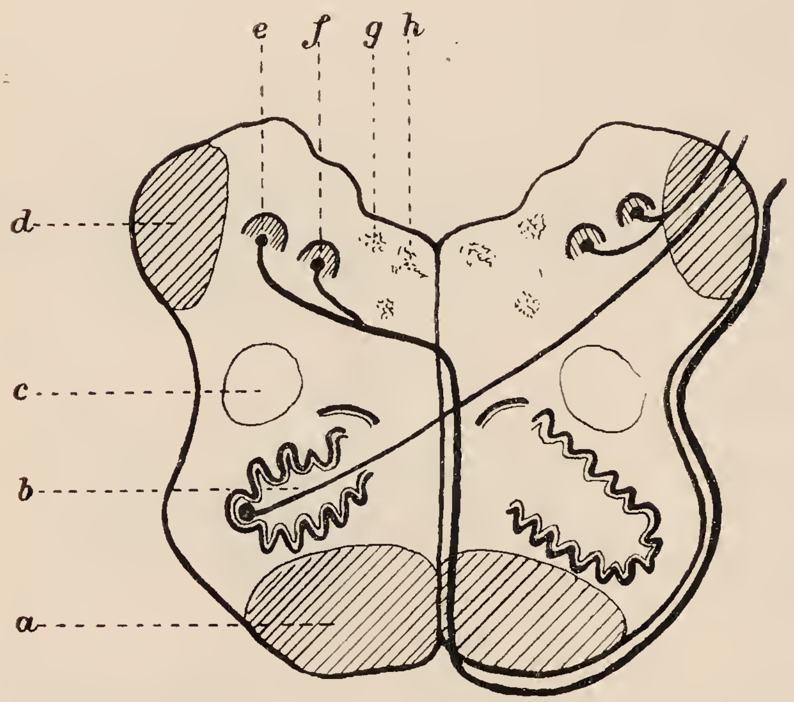


FIG. 18. — Diagram of upper part of medulla oblongata.

a, Pyramid; *b*, fibre from olivary nucleus; *c*, spino-thalamic fibres and Gowers' tract; *d*, restiform body; *e*, nucleus cuneatus; *f*, nucleus gracilis; *g*, nucleus of vagus; *h*, nucleus of hypoglossal nerve.

THE FUNCTIONS OF THE MEDULLA OBLONGATA.

Like the spinal cord, the medulla oblongata acts as a reflex centre or series of centres, and it also serves as a conducting path for impulses passing between the brain and spinal cord.

The reflexes which are carried out through the medulla oblongata are those concerned with the secretion of saliva and of the gastric and pancreatic juices; with the movements of the œsophagus, stomach, and intestine, including those involved in vomiting; with the regulation of the heart and blood-vessels; and with the regulation of respiration.

The physiological conducting paths in the medulla oblongata are (1) the motor path formed by the pyramid; (2) the rubro-spinal tract, lying dorsal to (4); (3) the chief sensory path, consisting of (*a*) the funiculus gracilis and funiculus cuneatus continued upwards from the spinal cord, (*b*) the cell stations in the nucleus gracilis and nucleus cuneatus, (*c*) the sensory decussation, and (*d*) the fillet, in which are also included the spino-thalamic fibres which have already crossed in the spinal cord; (4) the antero-lateral ascending tract, running upwards just behind the olivary nucleus; (5) the direct cerebellar tract running into the restiform body of its own side; (6) the vestibulo-spinal path, or posterior longitudinal bundle (medial longitudinal fasciculus), which lies in the formatio reticularis behind the fillet, and is concerned with the function of equilibration, connecting Deiters' nucleus and the nuclei of the third, fourth, and sixth cranial nerves with the spinal cord; (7) the spino-tectal fibres, which run upwards, forming part of the antero-lateral ascending tract.

THE PONS.

The outstanding feature of the structure of the pons is the presence of a large number of decussating nerve fibres, which pass backwards on each side to form the middle peduncles of the cerebellum. These transverse fibres occupy the ventral part of the pons, and split up the pyramid into a number of separate bundles (fig. 19). Behind them are the fillet and the formatio reticularis with the conducting paths described in connection with the medulla oblongata, these paths occupying much the same relative positions as they do in the medulla.

Lying posteriorly in the upper part of the fourth ventricle, and in or near the floor of the ventricle, are found the nuclei of the fifth, sixth, seventh, and eighth nerves. The upward continuation of the nucleus ambiguus forms the motor nuclei of the fifth and seventh nerves. The sixth nucleus, also motor, lies close to the floor of the fourth ventricle and near the motor nucleus of the facial. The sensory nucleus of the fifth nerve, lying laterally to the motor nucleus, receives some of the sensory fibres of this nerve. The other sensory fibres of the fifth

end in the spinal root. The cochlear division of the eighth nerve ends in two nuclei, which lie close to the restiform body, the accessory nucleus on its ventral aspect, and the *tuberculum acusticum* on its dorso-lateral aspect. The vestibular division of the eighth nerve ends partly in the chief vestibular nucleus in the floor of the fourth ventricle, and partly in the nucleus of Deiters, which lies laterally to the chief nucleus and is distinguished by the large size of its nerve cells.

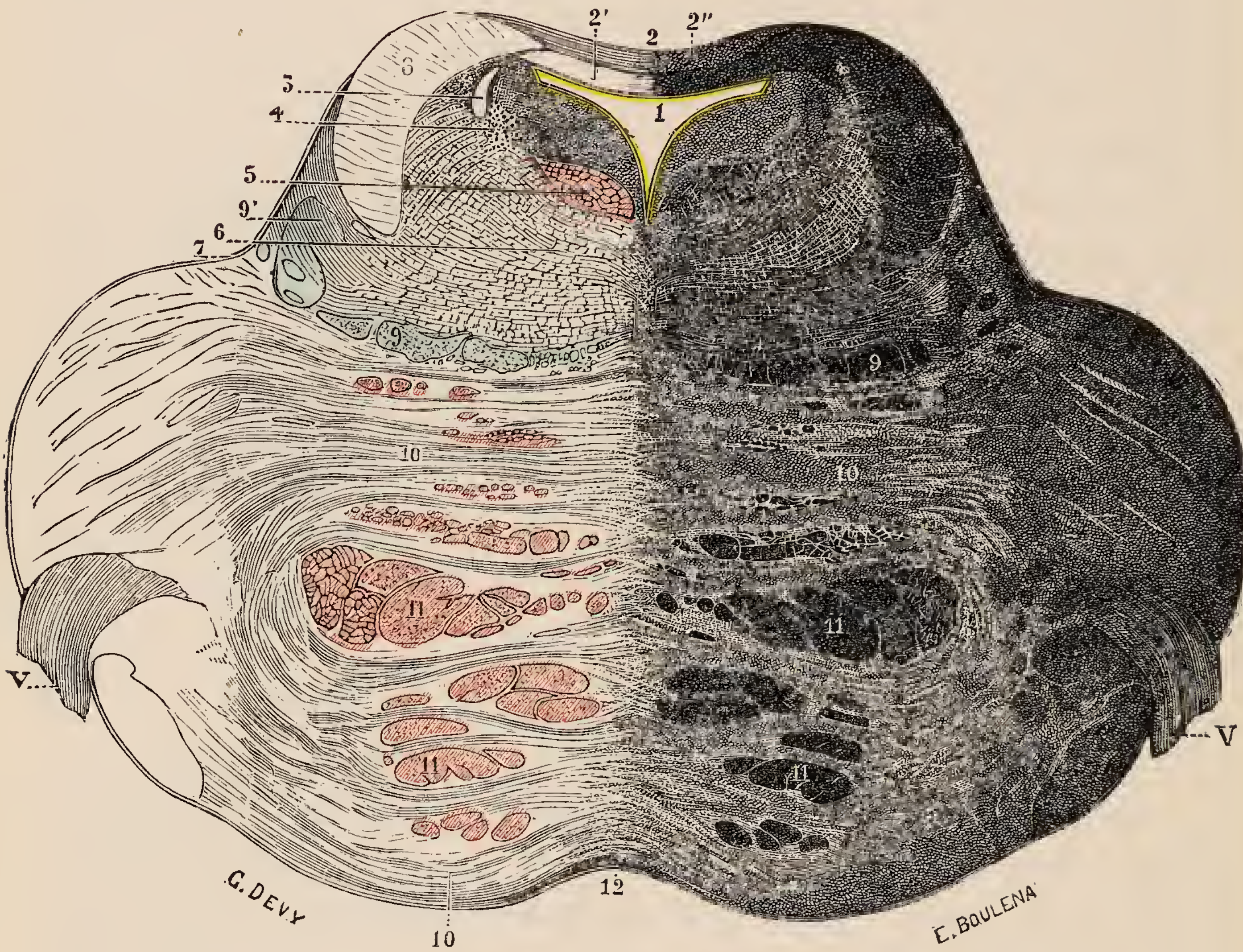


FIG. 19.—Coronal section of the pons, at its upper part. (Testut.) From Gray's *Anatomy.*

1, Fourth ventricle; 2, anterior medullary velum; 3, mesencephalic root of trigeminal; 4, nerve-cells associated with this root; 5, posterior longitudinal bundle; 6, formatio reticularis; 7, lateral sulcus; 8, section of superior peduncle; 9, medial lemniscus; 9', lateral lemniscus; 10, 10, transverse fibres of pons; 11, 11, pyramid; 12, raphe; V, exit of Vth nerve.

Groups of nerve cells, the *nuclei pontis*, lie among the transverse fibres in the ventral portion of the pons. These nuclei form a cell-station on the path of certain tracts which connect the cerebral hemispheres with the cerebellum. Axons from cells in the cortex of each cerebral hemisphere descend to the pons, where they arborise in relation with the nuclei pontis. The axons of the cells of the nuclei pontis become the transverse fibres of the pons, and cross the middle line to pass backwards and become the middle peduncles of the cerebellum.

THE FUNCTIONS OF THE PONS.

The nucleus of the sixth nerve and the motor nuclei of the fifth and seventh nerves receive efferent fibres from the cortex of the cerebral hemisphere, which have descended in the pyramid and crossed the middle line in the pons itself. Hence a unilateral lesion in the pons may be characterised by paralysis of the external rectus muscle of the eye and of the muscles of the face on the side of the lesion, along with paralysis of the arm and leg on the side opposite to the lesion.

The pons also forms the crossing place for the path, described above, of the fibres which connect one cerebral hemisphere with the cerebellar hemisphere of the opposite side.

The motor paths and the rubro-spinal tract pass through the pons, the former giving off fibres to the pontine motor nuclei in the manner already described.

The ascending tracts already described in connection with the medulla oblongata, with the exception of those which form the restiform body, pass through the pons unchanged. The fillet receives in its course additional fibres from the nuclei of the cochlear and fifth nerves.

The chief vestibular nucleus and the nucleus of Deiters are concerned with the function of equilibration. The axons of these nuclei divide into two groups, one group passing to the cerebellum in the restiform body, the other joining the posterior longitudinal bundle which links the oculo-motor and vestibular nuclei with the spinal cord.

SECTION VI.

THE CEREBELLUM.

The cerebellum is connected with the medulla oblongata and with the vestibular nuclei of the pons by the restiform body or inferior cerebellar peduncle on each side, with the pons by the two brachia pontis or middle cerebellar peduncles, and with the mid-brain by the two brachia conjunctiva or superior cerebellar peduncles. It consists of a middle lobe or vermis and two lateral lobes. The surface of the cerebellum is thrown into numerous folds, and the superficial layer, consisting of grey matter, is thus much increased in extent. The interior of the cerebellum is mainly composed of white matter, but it also contains some masses of grey matter, known as the nucleus dentatus, nucleus emboliformis, nucleus globosus, and nucleus fastigii.

The *cortical substance* consists of two layers with a single row of large nerve cells lying between them (fig. 20). These large cells are

known as the cells of Purkinje. They are flask-shaped, the axon coming from the base and the dendrons from the apex of each cell. The dendrons branch extensively, and the branches all lie in a plane

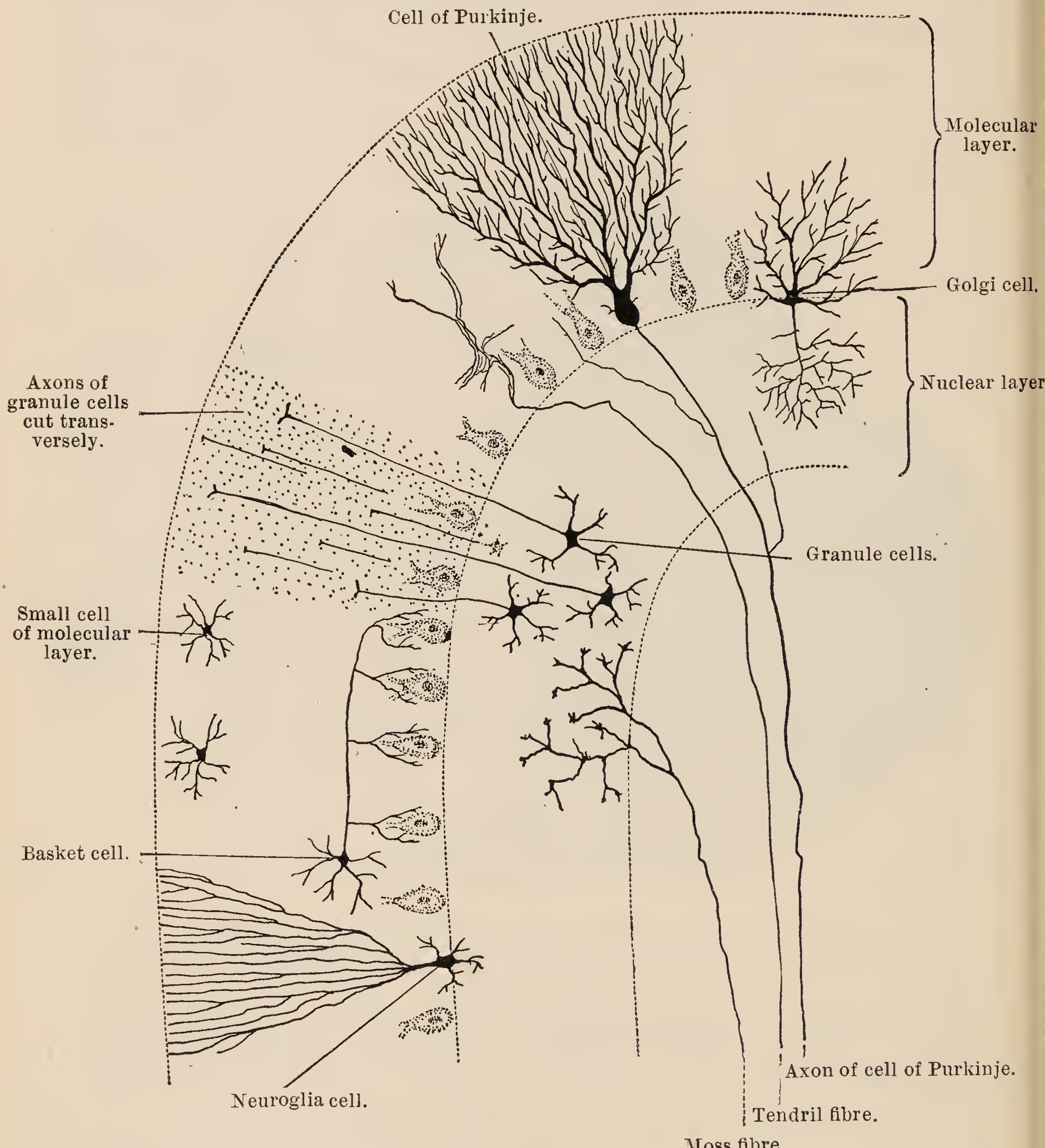


FIG. 20.—Transverse section of a cerebellar folium. (Diagrammatic, after Cajal and Kölliker.) From Gray's *Anatomy*.

across the direction of the fold or leaflet, so as to resemble a tree trained against a wall.

The inner (granular) layer contains a large number of small, rust-coloured nerve cells. The dendrites of these are short, and the axons pass into the outer layer, where they divide in a T-shaped manner, the

divisions running in the direction of the surface fold and thus crossing the dendrons of the cells of Purkinje at right angles. Afferent fibres from the white matter arborise round the cells of the granular layer, and are called moss-fibres because of the appearance of their terminations.

The outer layer of grey matter, or molecular layer, contains the dendrons of Purkinje's cells, the axons of the small cells of the internal layer, scattered nerve cells, and the terminations of afferent fibres from the white matter. The nerve cells of this layer are called basket cells, from the fact that their axons and the collaterals from the axons terminate round the cytons of the cells of Purkinje in a basket-like fashion. The afferent nerve fibres which reach the molecular layer arborise in apposition with the dendrons of the cells of Purkinje, and are hence known as climbing or tendril fibres. The Purkinje cells receive, therefore, three sets of afferent impulses, namely, (1) from the axons of the cells of the granular layer, (2) from the basket cells, and (3) from the tendril fibres.

The axons of the cells of Purkinje end in the nucleus dentatus, from which the impulses they transmit are passed on by other neurons.

The superior peduncles (brachia conjunctiva) pass to the mid-brain and run under the inferior colliculi. There the fibres of each cross the middle line and divide into ascending and descending branches. The ascending divisions end in the thalamus, the red nucleus, and the nuclei of the oculo-motor nerves. The descending divisions are believed to reach the anterior columns of the spinal cord. The brachia conjunctiva also convey the fibres of the antero-lateral ascending tract of the same side to the vermis of the cerebellum.

The brachia pontis form part of the connecting path between the cerebral hemispheres and the hemispheres of the cerebellum, the connection being a crossed one.

The restiform bodies contain both efferent and afferent fibres. The efferent fibres run from the nucleus fastigii and dentate nucleus to the nucleus of Deiters and the medulla oblongata. The afferent fibres are (1) the direct cerebellar tract from the same side of the spinal cord to the vermis; (2) fibres from the medulla oblongata, (*a*) from the nucleus gracilis and nucleus cuneatus of the same and the opposite sides, (*b*) from the olivary nucleus of the opposite side; and (*c*) from the formatio reticularis of both sides; (3) fibres from the chief vestibular nucleus and from Deiters' nucleus.

The cerebellum thus receives afferent fibres from the spinal cord, some direct through the restiform body, others by way of the superior peduncles, and other fibres which convey impulses from the spinal cord

but themselves arise in cell-stations in the medulla oblongata. It also receives afferent paths from the cerebral hemispheres, but whereas the connection with the cerebral hemispheres is a crossed one, that with the spinal cord is for the most part uncrossed.

The efferent fibres from the cerebellum are (1) those which run in the superior peduncles (brachia conjunctiva) to the mid-brain and thalamus, (2) fibres in the middle peduncles to the nuclei pontis, and (3) those which run in the restiform bodies to the vestibular nuclei and the medulla oblongata.

THE FUNCTIONS OF THE CEREBELLUM.

A knowledge of the cerebellar functions has been obtained partly by observation of the results of disease in man and partly by experiments on animals. When the normal impulses from the cerebellum are wanting, there is defective co-ordination of muscular movements as well as defective muscle tone. As a result, the power of maintaining the equilibrium of the body is impaired and the gait is staggering, though consciousness and volition are not affected. Further, observation of the results of localised lesions shows that different areas of the cerebellar cortex are associated with different groups of muscles, although no histological difference can be detected in the various parts of the cerebellar cortex. The cerebellum is, therefore, a reflex centre for the maintenance of muscle tone and for the co-ordination of muscular movements. It is especially concerned with the maintenance of the position of the body in relation to gravity, and with co-ordination of the movements of the body as a whole.

The effects of removal of the cerebellum, or of any part of it, vary according to the length of time that has elapsed since the operation was performed. The immediate effect of complete removal is chiefly a condition of ataxia or inco-ordination. If a pigeon, for example, shortly after removal of its cerebellum, attempts to fly, it only succeeds in making exaggerated and inco-ordinated movements of its wings. The attempts of a dog to walk under the same circumstances are equally futile. After some weeks or months, the animal regains the power of co-ordinated movement to a certain degree. The pigeon is able to fly and the dog to walk, but the power of movement is still greatly impaired. The condition is described as one of *asthenia*, *atonia*, and *astasia*, that is, there is loss of strength, loss of muscle tone, and unsteadiness of movement due to a condition of tremor accompanying attempts at muscular contraction. A dog is no longer able to walk with the normal diagonal movements of the limbs, but progresses by means of a series of jumps. The explanation of the partial recovery

is found in the fact that the cerebral hemispheres consciously direct the movements which, when the cerebellum is intact, are unconsciously co-ordinated. In this way, the cerebral mechanism compensates to some extent for the loss of cerebellar function. It will be remembered that two of the long tracts concerned with conveying afferent impulses from the muscles on each side terminate in the cerebellum, while the remaining two end in the thalamus, and are brought into relation with the cortex of the cerebral hemisphere by other neurons.

If one lateral half only of the cerebellum is removed, the weakness and tremors are limited to that side of the body. For two or three weeks the animal is unable to stand, and lies on the affected side with its head and trunk turned in the same direction (fig. 21). Later, it succeeds in standing and walking by abducting the limbs of the weak side or by availing itself of the support of a wall.

FIG. 21.—Dog with right half of its cerebellum removed. (From Schäfer's *Text-book of Physiology.*)

Stimulation of the cortex of the cerebellum gives rise to movements of the body, but stronger stimuli are required than in the case of stimulation of the cortex of the cerebral hemispheres. Weak stimuli applied to the central nuclei of the cerebellum are effective in producing movements, especially of the eyes and head. Stimulation of Deiters' nucleus in the pons, on the other hand, is followed by movements of the trunk and limbs.

Observation of the effects produced by localised lesions, experimental or pathological, shows that there is localisation of function in the cerebellar cortex. The immediate effect of such a partial injury is the occurrence of muscular contractions, giving rise to so-called "forced movements." Injury to the anterior part of the vermis is followed by movements of the head, injury of the anterior part of a lateral lobe by movements of the fore-limb of the same side, and injury of the posterior part of the lateral lobe by movements of the hind limb of the same side.

An additional fact which has some bearing on the function of the cerebellum is that in an animal from which the cerebral hemispheres have been removed, the cerebellum being intact, the muscles frequently pass into a condition of tonic contraction leading to what is known as decerebrate rigidity; this condition disappears on division of the posterior nerve roots.

Summary.—The cerebellum receives afferent impulses (1) by way of the vestibular nerve from the labyrinth of the ear, the end-organs in which are affected by changes in the position of the head, and (2) by the afferent nerves from the muscles, from the end-organs which are connected with muscle sense. Both these sets of impulses are known as proprio-ceptive to distinguish them from the extero-ceptive impulses conveying information as to the environment of the body. The cerebellum discharges efferent impulses which maintain muscle tone during rest, and which co-ordinate muscular movements during activity. These functions are especially of importance in the maintenance of equilibrium. The absence of the cerebellum is therefore attended by loss of tone and power in the muscles, as well as by a condition of inco-ordination or ataxia. Cerebellar ataxia is thus associated with muscular weakness, whereas spinal ataxia is associated with exaggerated muscular movements.

SECTION VII.

THE MID-BRAIN.

The mid-brain consists of the cerebral peduncles on its ventral aspect and the corpora quadrigemina on its dorsal aspect. The cerebral aqueduct runs through its substance and connects the third with the fourth ventricle. The cerebral peduncles contain the portions of the motor and sensory tracts which intervene between the fore-brain and the pons. The corpora quadrigemina are two pairs of prominences, the superior and inferior colliculi, seen on the dorsal surface.

If a coronal section is made through the mid-brain, it is seen that the cerebral peduncle is divided into a dorsal and a ventral portion by a layer of grey substance containing pigmented nerve cells and known as the *substantia nigra* (fig. 22). The portion of the peduncle ventral to the substantia nigra is called the pes (base), and it consists entirely of nerve fibres running longitudinally. The dorsal portion is known as the tegmentum. The fibres which form the middle three-fifths of the pes are the pyramidal fibres, and extend from the cortex of the cerebral hemisphere of the same side to become the pyramid of the medulla and the pyramidal tracts of the spinal cord. Some of the fibres, as has already been stated, cross in the hind-brain to the nuclei of the cerebral motor nerves. The fibres of the medial fifth of the base are the fronto-pontine fibres, and those of the lateral fifth are the temporo-pontine fibres, forming connections between the frontal and temporal cerebral lobes respectively and the nuclei pontis, and thus with the contralateral lobe of the cerebellum. The fibres which

lie dorsally to the substantia nigra form the upward continuation of the fillet, which is here bent at a right angle so that it is divisible into a medial and a lateral portion. The medial part is continued upwards to the thalamus, but the larger part of the lateral portion ends in the inferior colliculus of the corpora quadrigemina. The other tracts of fibres found in the tegmentum are the posterior longitudinal bundle (medial longitudinal fasciculus) and the superior peduncle. The tegmentum also contains a certain amount of grey matter, the greater part of which forms a well-defined group of nerve cells, known as the

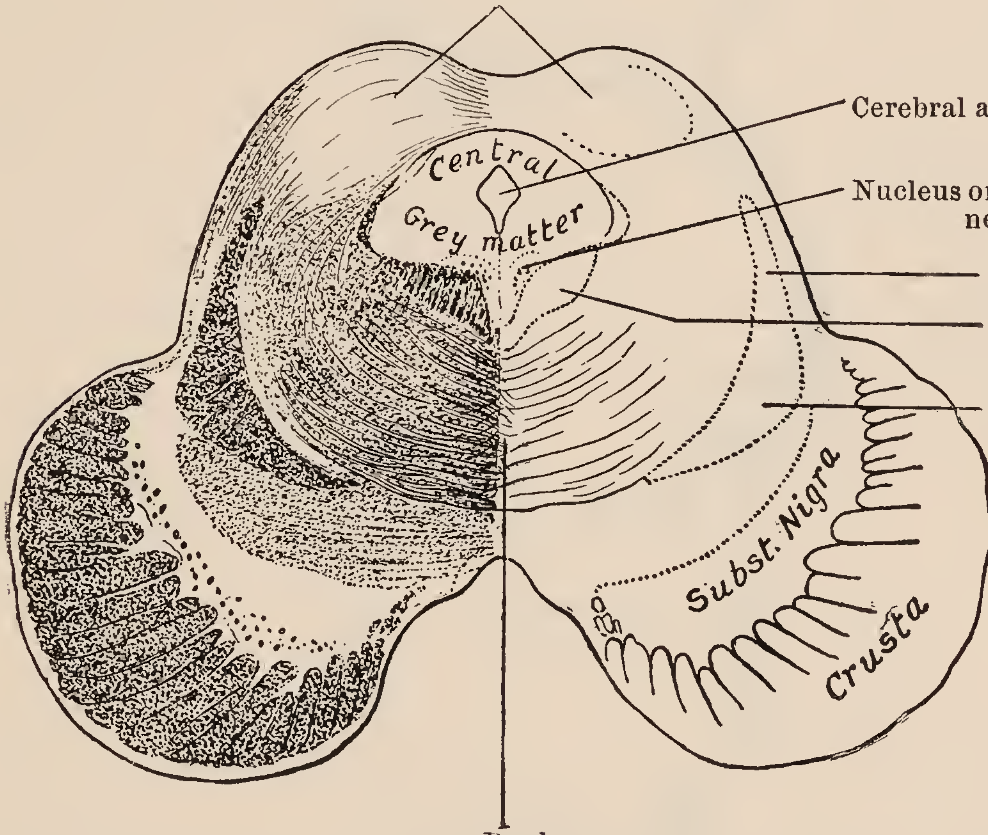


Fig. 22.—Transverse section of mid-brain at level of inferior colliculi. (Gray's *Anatomy.*)

red nucleus, lying near the middle line. The red nucleus gives origin to the fibres of the rubro-spinal tract, and receives most of the fibres of the superior peduncle.

The *corpora quadrigemina* are composed of grey matter, but the superior colliculi are covered by a layer of white fibres derived from the optic tract. Most of the fibres of the lateral fillet end in the inferior colliculus, the majority in that of the same side, some, however, crossing to the opposite side. The inferior colliculus is also connected by a bundle of fibres, the inferior brachium, with the internal (medial) geniculate body. Other fibres connect it, by way of the tegmentum, with the thalamus and the temporal lobe of the cerebral hemisphere. These various connections form part of the auditory tract. The lateral fillet conveys impulses from the nuclei of the cochlear nerve. These

are distributed to the inferior colliculus and internal geniculate body, and thence to the temporal lobe of the cerebral hemisphere.

The superior colliculus, on the other hand, is concerned with the function of vision. It receives fibres from the optic tract, which arborise round its nerve cells, and it gives origin to fibres which pass to the nuclei of the third (oculo-motor) nerve. It is also connected by

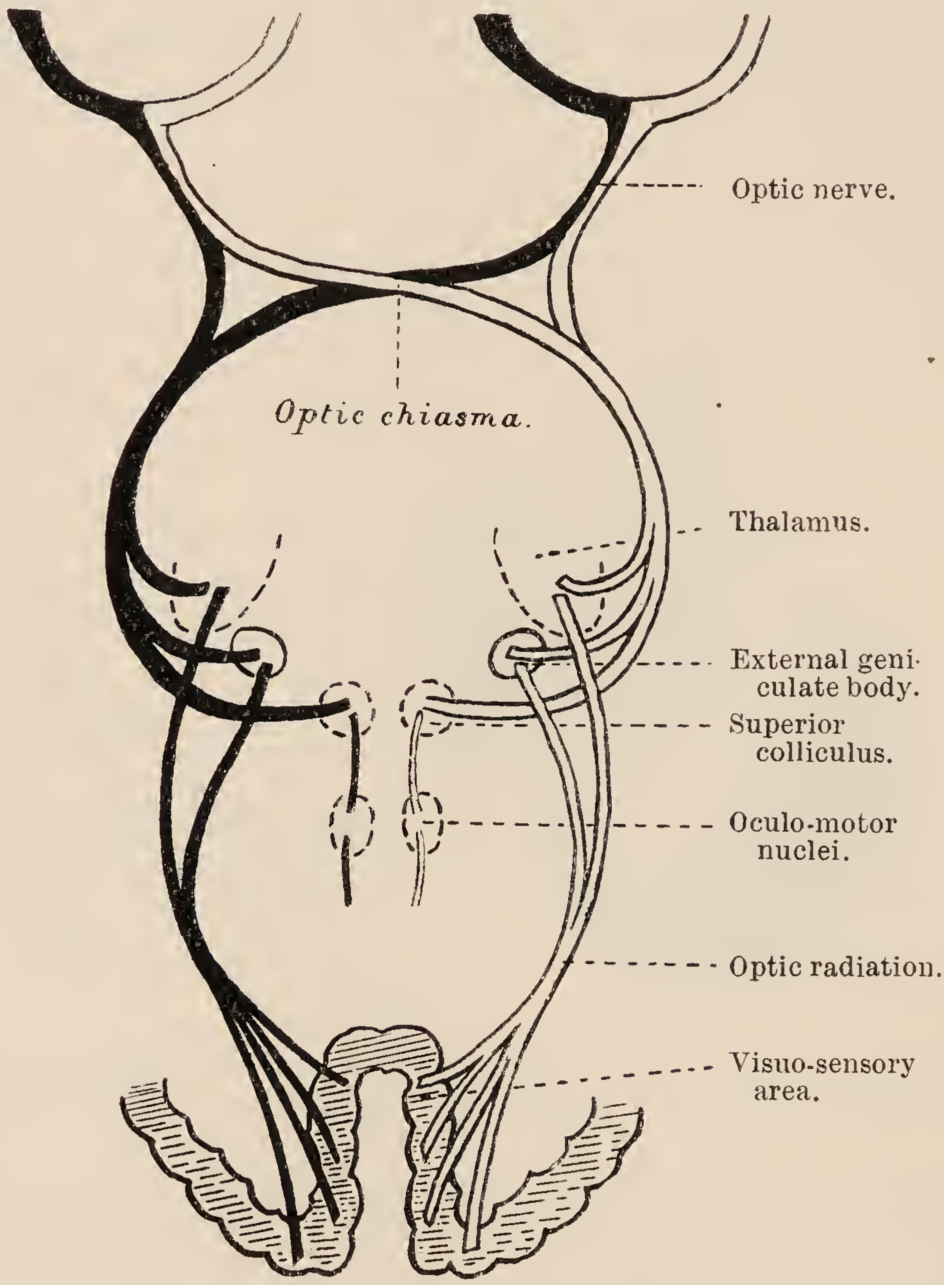


Fig. 23.—Diagram showing the path of the visual impulses.
The oculo-motor nuclei are connected by commissural fibres (not shown in figure).

a bundle of fibres, the superior brachium, with the external (lateral) geniculate body. The optic tract ends in cell stations in the superior colliculus, the external (lateral) geniculate body, and the thalamus (fig. 23). From the two latter of these stations, other neurons carry impulses to the cerebral cortex. The superior colliculus is also the place of origin of the tecto-spinal fibres, which are found in the anterolateral column of the spinal cord. These cross in the mid-brain by the fountain decussation of Meynert, and descend in the formatio reticularis of mid-brain, pons, and medulla oblongata.

The upward prolongation of the nucleus of the fifth nerve lies in the grey matter lateral to the cerebral aqueduct. The nuclei of the third and fourth nerves are found in the grey matter of the floor of the aqueduct. The posterior longitudinal bundle has a position immediately ventral to the latter nuclei. Some fibres of this bundle arise in a nucleus, the nucleus of the posterior longitudinal bundle, which lies at the upper part of the mid-brain, immediately under the thalamus. The bundle also receives a number of fibres from the superior colliculus. Its other connections have already been described.

The mid-brain, pons, and medulla oblongata together form the brain-stem, which conveys the conducting paths between the fore-brain and the spinal cord. In addition to its conducting function, the mid-brain forms a cell-station on the optic and auditory paths, and it also serves as a reflex centre for contraction of the pupil through the oculo-motor nucleus. It has also been suggested that the red nucleus may form a cell-station on an indirect motor path from the cerebral hemisphere to the spinal cord, the route being by way of the cerebro-cerebellar path through the pons, then by the superior peduncle to the red nucleus, and by the rubro-spinal tract from the latter to the spinal cord.

SECTION VIII.

THE FORE-BRAIN.

The fore-brain consists of the two cerebral hemispheres, together with certain masses of grey matter and other structures situated around the third ventricle, and comprising the thalami, the corpora geniculata, the hypophysis or pituitary body, and the pineal gland. The thalami and geniculate bodies are composed of grey matter. Each thalamus forms the lateral boundary of the third ventricle on its own side. The internal (medial) and external (lateral) geniculate bodies lie ventral to the thalamus on each side, and are in close relation with the superior colliculi.

The pineal gland lies immediately above the superior colliculi. It contains no nerve structure, being composed of alveoli with earthy phosphates in their interior, and it has not, so far as is known, any function. It is supposed to be the homologue of the pineal eye of the lizards.

THE CEREBRAL HEMISPHERES.

The cerebral hemispheres constitute the largest part of the brain. Each consists of an external layer of grey matter, thrown into folds or convolutions, with white matter internally. A mass of grey matter,

known as the *corpus striatum*, lies in the interior of each hemisphere, lateral to the thalamus and separated from it by a sheet of white matter, the internal capsule. Each hemisphere also contains in its interior a lateral ventricle, which is in communication with the third ventricle.

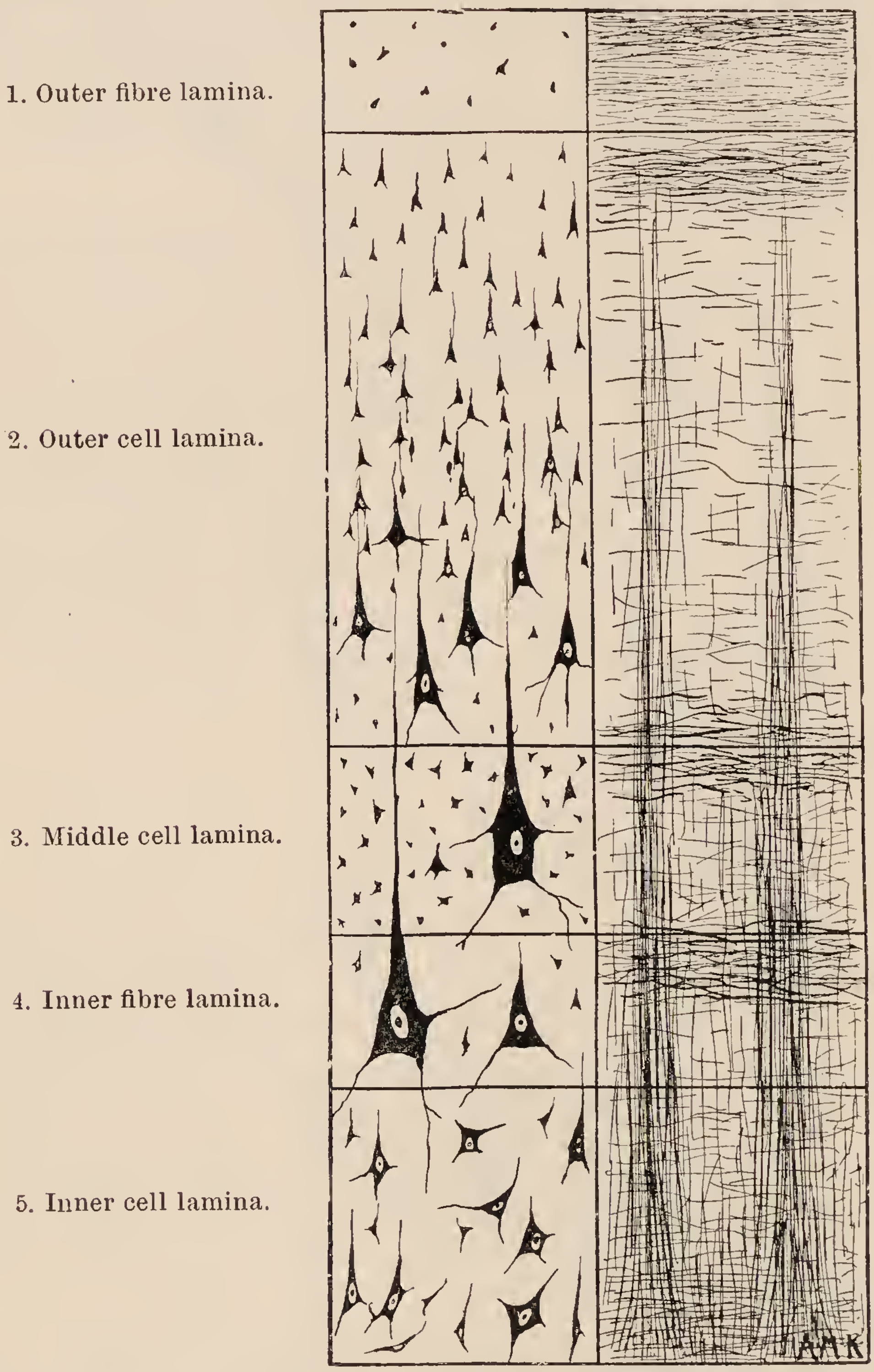


Fig. 24.—Structure of cortex of motor leg area. (Starling's *Principles of Physiology.*)

The grey matter consists of nerve cells and nerve fibres, arranged in layers. The axons of the nerve cells become either projection fibres or association fibres. Other fibres terminate by arborisation in the grey matter; some of these are projection fibres, most of which are axons of cells in the thalamus, and others are association fibres, proceeding from cells in other parts of the cortical layer.

The structure of the grey matter varies in different regions of

the cerebral hemisphere, but, whatever the local modifications, the general plan is the same in all parts, and shows an arrangement in five layers (fig. 24). These layers are named as follows:—

(1) The outer fibre lamina, or molecular layer.
(2) The outer cell lamina.
(3) The middle cell lamina, or granule layer.
(4) The inner fibre lamina.
(5) The inner cell lamina, or layer of polymorphic cells.

A convenient modification of this description is to speak of the layers in their relation to the middle cell lamina or layer of granules. This arrangement gives (1) a supragranular layer, consisting of a fibre lamina and a cell lamina; (2) the granule layer itself; and (3) an infragranular layer, consisting of a fibre lamina and a cell lamina.

The outer fibre lamina contains medullated nerve fibres running horizontally, a few scattered nerve cells, and the dendrons of many of the cells of the next layer.

The outer cell lamina contains pyramidal nerve cells, and may be subdivided into layers of small, medium, and large pyramids, the small pyramids being most superficial, and the large pyramids most deeply situated.

The middle cell lamina contains pyramidal cells, but is especially characterised by the presence of a large number of stellate cells, some of which are large and others small.

The inner fibre lamina consists of medullated nerve fibres, running horizontally, but in the motor area it contains also large and often solitary pyramidal nerve cells, called Betz cells, the apical dendrons of which may extend to the outer fibre lamina.

The inner cell lamina contains a large number of irregular or polymorphic cells, as well as some pyramidal cells, the cells of Martinotti, the apices of which point centrally, while the axons pass towards the surface.

The Functions of the Cell Layers.—Information may be obtained as to the function of the different cell layers of the grey matter in three ways: (1) by observing the order of their development in the child; (2) by a comparison of their relative proportion in man and in the lower animals; and (3) by a comparison of the different regions in the human adult cerebrum, and by observations of the differences in persons suffering from amentia or dementia.

(1) The study of development of the cortex shows that the inner cell lamina is the first to appear, and that it has attained three-fourths of the adult depth at the sixth month of fœtal life. It is followed by the middle cell lamina, which, however, has only one-half of the adult

depth at the sixth month of fœtal life. The outer cell lamina is the last to appear, and develops slowly after birth. The outer fibre lamina is well developed at birth, and is associated in its further growth with that of the outer cell lamina. The inner fibre lamina is well developed at birth, attaining its adult depth almost at once.

(2) The inner cell lamina is the first to appear in the evolution of the cerebral cortex, and is well developed in the lower mammalia; in the mole, for example, it forms the greater part of the depth of the cortex. It is followed by the middle cell lamina, the outer being the last to appear, and attaining a low degree of development in all animals below man. The outer cell lamina, however, increases progressively in depth from the insectivora through the rodents and ungulates to the carnivora.

(3) The least developed portion of the human cerebral cortex is the grey matter of the hippocampus, in which the only cell laminæ represented are the middle and inner. The ascending frontal convolution (motor area) is characterised by the presence of Betz cells in the inner fibre lamina. The visuo-sensory area, situated in the occipital lobe, is distinguished by an increase in depth of the middle cell lamina. The outer cell lamina is most highly developed in what are known as the association areas. These are three in number: the posterior, occupying the posterior part of the parieto-temporal region; the middle, in the island of Reil; and the anterior, which lies in that part of the frontal lobe known as the pre-frontal region. The pre-frontal region is the highest zone of association, and in it the outer cell lamina undergoes the greatest development, varying considerably, however, in different individuals. The outer cell lamina in this region is more or less pronounced according as the mental development is of greater or less degree. It is imperfectly developed in idiots and imbeciles, and its cells are atrophied in cases of dementia.

On the basis of these facts, J. S. Bolton ascribes different functions to the three cell laminæ. The polymorphic layer subserves the instinctive activities concerned with obtaining food and shelter, with seeking protection from danger, and with the functions connected with sex. The middle cell lamina is concerned with the reception and transformation of afferent impulses. The outer cell lamina is psychic or associational, and has to do with the mental processes, especially with those included under the terms "voluntary attention" and "inhibition."

THE TRACTS OF THE CEREBRAL HEMISPHERES.

The nerve fibres of the white matter of the cerebral hemispheres are either projection fibres or they are associational in character, including under the latter term the commissural fibres which connect

the two hemispheres. The projection fibres are those which connect the cerebral cortex with the lower parts of the central nervous system, and they are either afferent or efferent. The associational fibres link up different parts of the cortex. The fact that nerve fibres acquire their myelin sheaths at the time at which they become functionally active has been made use of by Flechsig in studying the nerve tracts of the cerebral hemispheres, and, from his observations, he has come to conclusions as to the functions of the different areas of the cortex which are as a whole identical with those based upon the study of the structure of the grey matter in different regions of the adult cortex. The first fibres to become myelinated in the cerebral hemispheres are those afferent projection fibres which are distributed to the sensory areas of the brain. The last to acquire a myelin sheath are those which are connected with the higher centres of association.

The Projection Fibres.—The *efferent* projection fibres are the pyramidal (cerebro-spinal) and the cerebro-cerebellar. The *pyramidal fibres* are the axons of the Betz cells in the pre-central convolution or motor area. They converge towards the base of the hemisphere, and occupy the genu and the anterior two-thirds of the posterior limb of the internal capsule (fig. 27). From this situation they descend in the pes of the cerebral peduncle and through the pons and medulla oblongata to the spinal cord in the manner already described.

The *cerebro-cerebellar fibres* are the fronto-pontine from the frontal lobe and the temporo-pontine from the temporal lobe. These descend, the former in the anterior limb of the internal capsule, the latter in the posterior third of its posterior limb, to the base of the cerebral peduncle, after passing through which they reach the pons to arborise round the cells of the nuclei pontis.

The *afferent projection fibres* are the thalamo-cortical, the optic radiation, the auditory radiation, and some fibres of the superior cerebellar peduncle.

The *thalamo-cortical* fibres form the final relay on the path of afferent impulses from the lower centres to the cortex of the cerebral hemisphere, and they are distributed to all parts of the cortex. The thalamo-frontal fibres run towards the frontal lobe in the anterior limb of the internal capsule. The thalamo-parietal fibres pass through the posterior limb of the internal capsule to reach their destination in the parietal lobe. Those to the island of Reil run under the lenticular nucleus. Those to the temporal lobe run in the posterior end of the posterior limb of the internal capsule, and are joined by other fibres from the inferior colliculus of the corpora quadrigemina and the medial geniculate body to form the auditory radiation. Those to the occipital

lobe run in the internal capsule behind the auditory radiation, and are joined by other fibres from the external geniculate body to form the optic radiation.

Some of the fibres of the superior cerebellar peduncle have cell stations in the thalamus, but others are believed to pass through the posterior end of the internal capsule without interruption to end in the cortex in the neighbourhood of the central sulcus or fissure of Rolando.

The Association Fibres.—The *short association fibres* lie immediately under the cortex and connect the grey matter of adjacent convolutions. The *long association fibres* form tracts which unite areas of the cortex which are at some distance from each other. One tract, the superior longitudinal fasciculus, runs between the frontal and occipital lobes; another, the inferior longitudinal fasciculus, connects the temporal and occipital lobes; a third, the uncinate fasciculus, connects the frontal and temporal lobes; a fourth connects the parietal and occipital lobes; while a fifth runs from the anterior perforated space (substance) over the corpus callosum to the hippocampus.

The *commissural fibres* connect the two cerebral hemispheres and are grouped in the corpus callosum, and the anterior, posterior, and hippocampal commissures. The corpus callosum contains fibres from all parts of each cerebral hemisphere except the olfactory bulb and parts of the temporal lobe. The olfactory lobes are connected by the anterior and hippocampal commissures, the anterior commissure also containing fibres which connect the two temporal lobes. The relationships of the posterior commissure are unknown.

The association and commissural fibres are either axons of cells in the grey matter of the cortex or collaterals from axons; they terminate by arborisation in relation with other nerve cells.

THE FUNCTIONS OF THE CEREBRAL HEMISPHERES.

The ascent of the animal scale is marked by a progressive increase in the size and development of the cerebral hemispheres, and in man these structures are absolutely and relatively larger than in any of the lower animals. This increase in size is associated with a corresponding increase in functional importance, the higher centres acquiring a more marked control over those in the spinal cord. This fact becomes more apparent when the results of removal of the cerebral hemispheres in different animals are compared. In the case of the frog, when the animal has recovered from the shock of the operation, there is at first sight little difference from the normal condition. The posture is normal, equilibrium is maintained, and is regained if the frog is placed

on its back. When the animal is placed in water, it swims to the margin and crawls out; if it is placed on an inclined plane, it crawls to the top and balances itself there. If, however, it is not stimulated in any way, it will remain in the same attitude until it dies. The complicated reactions known as volitional impulses are wanting, and the frog shows no spontaneous movements.

Similar phenomena may be observed in a pigeon from which the cerebral hemispheres have been removed. There is the same maintenance of posture unless the animal is disturbed; and the power of equilibration is not affected. The pigeon flies in a normal manner if it is thrown in the air, but it soon alights and resumes its resting attitude. It pecks at the ground if it is hungry, but does not feed itself.

The removal of the cerebral hemispheres in mammals is usually followed by a fatal result, but Goltz succeeded in performing the operation in a dog by carrying it out in successive stages; and he afterwards kept the animal alive for a year and a half. Temporary paralysis followed, but was recovered from, and thereafter, in marked contrast with the frog and pigeon under similar circumstances, the dog showed a tendency to be in continual restless movement. It even learned to feed itself when food was placed near its nose. It responded to stimuli, if painful, by growling or barking and turning its head towards the stimulated spot, though it showed no sign of recognition of the persons who fed it, and gave no indication of fear when threatened or of pleasure when caressed.

The absence of the cerebral hemispheres, therefore, in the frog, pigeon, and dog is associated with a condition in which the animal responds to stimuli in a more direct and simple fashion than is the case when the brain is intact. In the normal animal, the effect of a stimulus is modified by impulses arising out of the memory of previous experiences. When the cerebral hemispheres have been removed, the memory records are absent, and the response to the stimulus is simplified; in other words, there is an absence of intelligence, of volition, and of emotion. But the machinery for the carrying out of muscular movements in a co-ordinate manner still remains, and can be set in action by a suitable stimulus.

The function of the cerebral hemispheres is therefore associative, combining the effects of immediate with those of past stimuli, and giving out efferent impulses based on such combinations. The grey matter of the cortex is not only excited by stimuli, but the stimuli produce a permanent record in its cells, known as memory, which exercises an important influence on all subsequent actions.

THE LOCALISATION OF FUNCTION IN THE CEREBRAL HEMISPHERES.

It has already been pointed out that histological and embryological researches have indicated that different areas of the cortex subserve different functions, and both observation of the results of disease in man and experimental studies in connection with animals have confirmed and extended these conclusions. Injuries and tumours of different parts of the human cortex give rise to muscular paralysis, blindness, deafness, aphasia, or mental deficiency, according to the site of the lesion. Experiments carried out on animals, either of the nature of stimulation of various parts of the surface of the cerebral hemispheres or of removal of localised portions, have given results parallel with those derived from the study of diseases and injury in human beings; and as a consequence it has been possible to map out the surface of the hemispheres into areas, each of which possesses a definite function. The pre-central convolution is motor in function, the post-central is sensory and is especially concerned with the reception of kinæsthetic impulses, that is, impulses from muscles, tendons, and joints, and with tactile discrimination. The mesial aspect of the occipital lobe, or that part of it which lies on the borders of the calcarine fissure, is visuo-sensory, while the convolutions immediately adjacent to the visuo-sensory area are visuo-psychic. The audito-sensory area and the audito-psychic areas are situated in the superior temporal convolution. The area for taste and smell is in the hippocampal convolution. No special area has been discovered for the senses of heat, cold, pain, and tactile localisation. The parieto-temporal region, the island of Reil, and the pre-frontal region form the three special association areas (fig. 25).

The Motor Area.—Stimulation of either the grey matter or of the underlying white matter of the pre-central convolution gives rise to muscular movements on the opposite side of the body. The latent period is longer for stimulation of the grey matter than when the white fibres are excited, but a stronger stimulus is required to elicit movement from the white matter than from the grey. In either case the resulting movements are co-ordinated, groups of muscles being affected, and contraction of a particular group being accompanied by reciprocal relaxation of the corresponding antagonistic group. In other words, "movements, not muscles" are represented in the cortex. Further, stimulation of a particular point in the pre-central convolution is invariably followed by the same movement, so that, for example, excitation of one point will result in extension of the thigh, of another in flexion

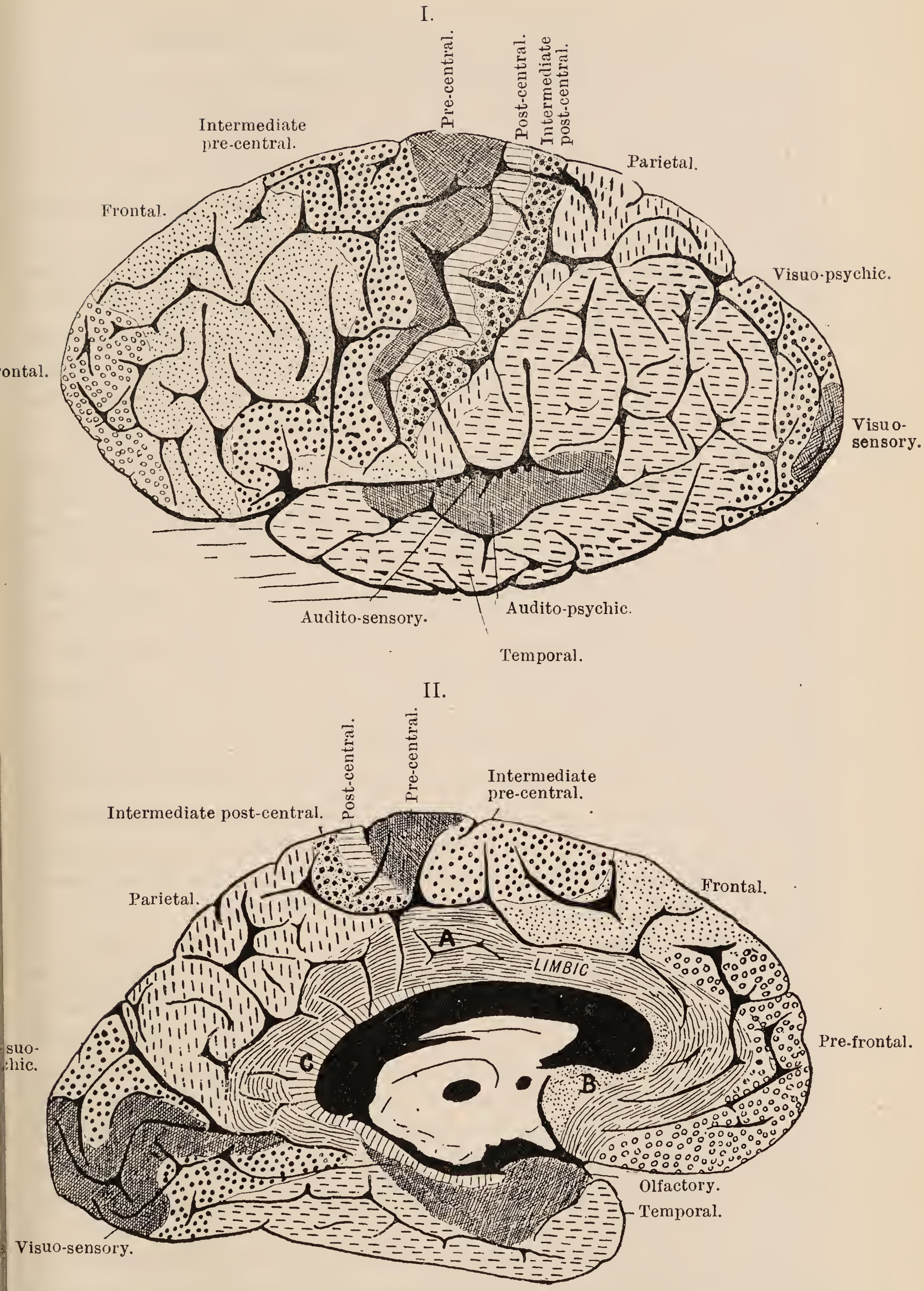


FIG. 25.—Diagrams (orthogonal) of cortical areas as determined by the distribution and arrangement of fibres and cells. (A. W. Campbell.) From Quain's *Anatomy*.

I., lateral surface; II., mesial surface.

of the thigh, of another in flexion of the leg, and so on. The representation of the movements of the leg, trunk, arm, and face is in that order on the convolution from above downwards, and each of these sub-areas may be further subdivided into points for the movements of particular groups of muscles.

Correlated with the development of the cerebral cortex is the increased size of the pyramidal tract, which in monkeys, and still more in man, is the principal path for the rapid conduction of voluntary impulses to the motor neurons of the spinal cord. Other motor paths from the cerebral cortex probably exist in the human nervous system, but have fallen into disuse, and it is for this reason that the effects of lesions of the cortex or of the pyramidal tracts in any part of their course are so much more severe and permanent in man than in the lower animals.

It must not be supposed that the motor area of the cerebral cortex is the actual seat of voluntary impulses. On the contrary, its activity is aroused by impulses from other parts of the brain, and represents only a small fraction of the total process of which it forms a part. Generally speaking, the movements produced are on the opposite side of the body to that stimulated, but in some cases muscles on both sides of the body may be simultaneously affected; for example, stimulation of a point concerned with the movements of the eyes will result in both eyes being turned towards the opposite side. If the right side be stimulated, the eyes are turned to the left by the contraction of the right internal rectus and the left external rectus, with simultaneous relaxation of the right external and left internal recti. Similarly the areas for the trunk and neck govern movements of both sides of the body. In all cases in which a movement is carried out by the combined action of muscles on the two sides of the body, the muscles of both sides are bilaterally represented in the cortex.

If a stronger stimulus is applied to a motor point on the cortex than is necessary to elicit the movement peculiar to that point, the excitation will spread to adjacent areas, just as irradiation occurs in the spinal cord. By increasing the strength of the stimulus it is possible to throw all the muscles of the body into convulsive contractions. A similar phenomenon is exhibited in Jacksonian epilepsy, in which a localised irritation of a motor area, such as that due to the pressure of a spicule of bone, causes a general convulsion beginning in the part of the body represented at the site of the lesion.

The motor area has been stimulated in conscious human beings; the stimuli elicited movements without any sensation other than a consciousness of the movements which took place. There is therefore no reason

to ascribe any sensory function to the pre-central convolution, and it must be considered as purely motor.

The effect of removal of the motor area varies in different animals. In all cases the immediate effect is paralysis of the muscles on the opposite side of the body. In the dog recovery takes place, and the power of movement becomes almost as complete as it was before the operation. In the monkey recovery is less complete, and a certain degree of weakness may remain as a permanent result. When the motor area or any part of it is destroyed by disease in man, recovery is still less complete. In the ascent of the animal scale the functions of the nervous system become more and more transferred to the higher centres; hence injury of these centres in the higher animals, and especially in man, is productive of more serious interference with the neuro-muscular mechanism than is the case in animals lower in the scale.

The Area for Skin and Muscle Sense.—It is obviously a matter of considerable difficulty to locate the area for tactile and muscular sensibility, inasmuch as stimulation of a sensory area in animals is followed by no objective phenomena, and opportunities rarely arise for observation of the results of stimulation in conscious human beings. There are, however, recorded cases of stimulation of the post-central convolution in conscious individuals, and in these sensations of numbness and touch were evoked. Apart from stimulation, the localisation of the sensory areas rests upon the effects of removal, the distribution of the thalamo-cortical fibres which represent the upward continuation of the fillet, and histological and clinical observations.

Stimulation of the post-central convolution in animals is followed by muscular movements, but a stronger stimulus is required to elicit these than is necessary if the pre-central convolution is stimulated, and the latent period is longer in the case of the post-central, indicating that the impulse has to traverse a larger number of neurons. This result is what might be anticipated, as it is probable that the post-central and pre-central convolutions are connected by short association fibres.

Removal of the post-central convolution in monkeys is said to result in ataxia of the muscles of the opposite side of the body without paralysis. On the other hand, Graham Brown has excised a part of the post-central convolution opposite the arm area of the pre-central in a young chimpanzee, and records that after a short period of weakness of the opposite fore-limb there was no appreciable permanent motor defect.

The thalamo-cortical fibres are distributed not only to the post-central convolution but also to the temporal, frontal, and occipital lobes, and therefore sensory impulses are distributed to a much wider

area of the cortex than that from which motor impulses arise. The chief tract of thalamo-cortical fibres, however, terminates in the post-central gyrus.

The available evidence indicates, therefore, that the post-central gyrus is a sensory area specially connected with the tactile and muscular senses, and that the senses of heat, cold, and pain have a wider distribution on the cortex of the cerebral hemisphere, corresponding with their wide distribution on the surface of the body.

The Visual Area.—The visuo-sensory area occupies the greater part of the mesial aspect of the occipital lobe, the visuo-psychic area surrounding it and extending on to the lateral aspect of the lobe.

Extirpation of both occipital lobes results in total blindness, extirpation of one lobe leading to blindness of the homolateral half of each retina. Stimulation of the visuo-sensory area is followed by movements of the eyes. From the direction in which the eyes are turned in response to stimuli applied to various parts of the area, it may be inferred that the retinal impulses are projected on to the cortex according to a definite plan. Thus stimulation of the upper part of the occipital lobe is followed by a downward movement of the eyes, while stimulation of a lower point of, say, the right lobe leads to a deviation of both eyes towards the left. In the former case the movement is that which would normally follow the excitation of the upper part of the retina, in the latter it is that which would occur from excitation of the right side of either retina. The fovea centralis, or part of the retina concerned with distinct vision, is represented bilaterally.

Impulses are transmitted from the retinæ to the occipital lobes by the optic nerves, optic tracts, and optic radiations. Each optic nerve, consisting of the axons of nerve cells in the retina, divides at the chiasma, the fibres from the mesial side of the retina crossing to the opposite side to take part in the formation of the optic tract of that side. Thus each optic tract is made up of fibres from its own side of each retina. The tract fibres terminate by arborisation in the pulvinar of the thalamus, the external geniculate body and the superior colliculus of the corpora quadrigemina. The fibres which enter into the optic radiation arise in the thalamus and external geniculate body, and are distributed to the cortex of the occipital lobe (fig. 23). The relay fibres from the superior colliculus are distributed to the oculo-motor nuclei, and appear to be concerned with the function of equilibration and with reflex contraction of the pupil.

The Auditory Area.—The localisation of the auditory area is less definite than that of the visual area, largely owing to the difficulty of ascertaining the degree of deafness produced in animals by experimental

lesions. A partial decussation of the auditory tracts occurs, similar to that of the optic nerves, so that each cerebral hemisphere receives impulses from both ears.

The audito-sensory area is located in the temporal lobe, and has been supposed to be limited to the middle region of the superior temporal convolution, the audito-psychic area being adjacent to it. But whereas, so far as can be judged, extirpation of one temporal lobe is followed by partial deafness, and removal of both lobes by complete deafness, Schäfer has shown that removal of the superior temporal convolutions alone from both sides in monkeys does not result in complete deafness. The superior temporal convolution is probably the chief centre for hearing, but there may be subsidiary areas outside it.

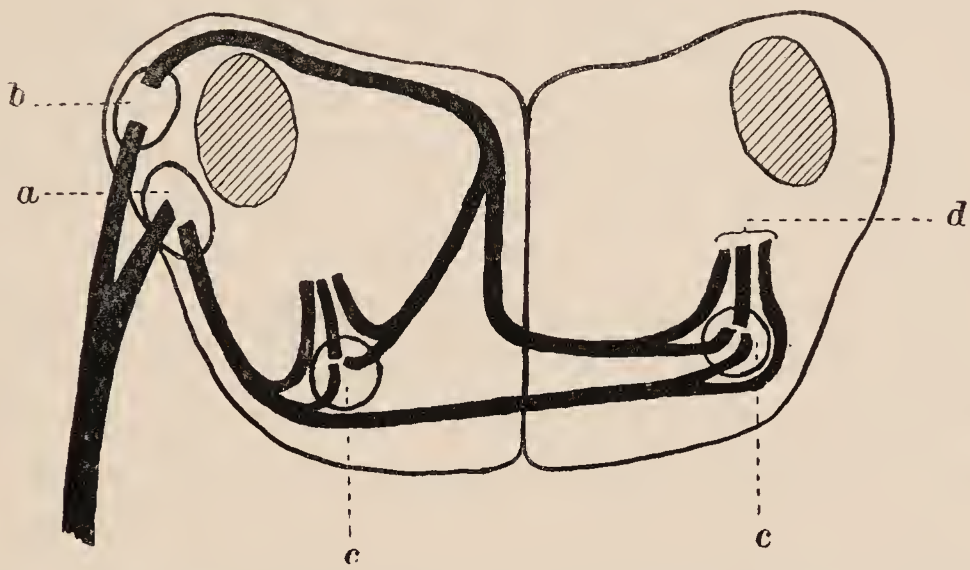


FIG. 26.—Diagram showing the paths for auditory impulses in the pons. *a*, Accessory nucleus ; *b*, tuberculum acusticum ; *c*, trapezoid nucleus ; *d*, lateral fillet.

Stimulation of the superior temporal convolution in monkeys is followed by pricking of the opposite ear and turning of the head towards the opposite side.

Impulses are conveyed from the cochlea to the auditory centre by the cochlear division of the eighth nerve, the auditory tract, and the auditory radiation. The fibres of the cochlear nerve are derived from the spiral ganglion, and terminate in the tuberculum acusticum and the accessory nucleus. The axons from the tuberculum acusticum turn over the restiform body to become the *striæ acusticæ* (*striæ medullares*) in the floor of the fourth ventricle. These dip into the substance of the pons at the middle line, some passing to the trapezoid nucleus and superior olivary nucleus of the same side, others to the corresponding nuclei of the opposite side. Some fibres terminate in these nuclei on each side, others are continued directly into the lateral fillet. The fibres from the accessory nucleus constitute the trapezium, and also enter into the formation of the lateral fillet (fig. 26). Many of the trapezoid

fibres have cell stations in the trapezoid and superior olivary nuclei. The lateral fillet terminates in the inferior colliculus and internal geniculate body; from the latter new fibres arise to be distributed to the superior temporal convolution as the auditory radiation.

The Area for Smell and Taste.—The area for smell and taste is located in the hippocampal convolution and the neighbouring structures. Extirpation of this area has not yielded definite results. Stimulation causes movements of the lip and nostril on the same side, such as would be caused by a disagreeable or irritating odour applied to the nostril. Further information is derived from a comparative study of the degree of development of these parts of the brain in animals which have, and others which have not, a highly developed sense of smell.

The olfactory nerve fibres are non-medullated processes of cells in the olfactory mucous membrane, and terminate in structures known as glomeruli in the olfactory lobe in relation with the dendrites of certain "mitral" cells, the axons of which convey the impulses transmitted to them by the olfactory fibres to the hippocampal region of the same or the opposite side.

The nerves of taste are the chorda tympani to the anterior two-thirds and the glossopharyngeal to the posterior third of the tongue. The taste fibres of both nerves terminate in a column of cells in the pons, which also receives afferent fibres from the fifth nerve. The conducting tract from this nucleus to the cortical area for taste has not been traced.

The Association Areas.—There are three great association areas: the posterior in the parieto-temporal region, the middle in the island of Reil, and the anterior or pre-frontal. Stimulation of these areas gives rise to no obvious motor response, but disease or imperfect development in man is accompanied by various forms of mental deficiency. The pre-frontal area is the highest associational centre; it is the last to develope and the first to retrograde. In it the outer cell lamina attains its greatest depth, and atrophy of the cells of this lamina is found in cases of dementia. The posterior association area, lying between the visuo-psychic and the audito-psychic areas, is concerned with mental images, especially with the processes involved in the perception of spoken and written language. Lesions of this area are accompanied by interference with the appreciation of words, the different forms of sensory aphasia.

The human brain is characterised by the great development of the association areas. They represent the material basis for the memory of past stimuli, and for the comparison of one set of stimuli with another. In other words, they are the anatomical structures concerned

with knowledge, intelligence, and, still further, with the faculties of inhibition and voluntary attention, which find their highest development in man.

SPEECH AND APHASIA.

The pre-eminence of man is intimately related with the power of speech or the use of words as symbols to awaken the memory of past stimuli. The production of spoken or written words is of course only a specialised use of the muscular system; but for the appreciation of language the existence of word-hearing and word-seeing centres has sometimes been assumed. It is found that aphasia or loss of the power of speech may take several forms. Thus there may be *motor aphasia*, in which the power of forming words is lost, or *sensory aphasia*, in which there is inability to comprehend spoken or written language.

Motor aphasia was formerly ascribed to a lesion of the third left frontal (Broca's) convolution, but it has been ascertained that the actual cause of the aphasia in such a case is destruction of the sub-cortical fibres in the neighbourhood of the lenticular nucleus, along with some degree of sensory aphasia. The term *anarthria* is applied to the loss of power of articulate speech due to a lesion of the sub-cortical motor fibres. Sensory aphasia may take the form of word-blindness or word-deafness. In word-blindness, vision may be perfect and the words on a printed page may be distinctly seen, but they are as meaningless as if they were in an unknown language, and there is no power of associating the written symbol with past stimuli. Similarly in word-deafness, hearing may be perfect, but spoken words are unintelligible sounds. Anarthria may occur without any loss of intelligence, but sensory aphasia is always accompanied by some degree of mental deficiency, especially in the case of word-deafness.

THE THALAMUS AND INTERNAL CAPSULE.

The thalamus forms the lateral boundary of the third ventricle. It is a large ganglionic mass and receives the terminations of the fibres of the fillet. The outgoing fibres from the thalamus are distributed to all parts of the cortex of the cerebral hemispheres, and cortico-thalamic fibres also run from the cortex to the thalamus. On the lateral aspect of the thalamus is the internal capsule, to and from which fibres radiate from and to all parts of the cortex. In a horizontal section, the internal capsule is seen to consist of a short anterior limb pointing outwards and forwards, and a longer posterior limb pointing outwards and backwards; the junction of the two limbs is termed the genu.

The lateral aspect of the internal capsule is bounded by the lenticular nucleus of the cerebral hemisphere. The anterior limb is bounded on its mesial aspect by the head of the caudate nucleus of the hemisphere. The anterior limb of the internal capsule contains the fronto-pontine fibres. The genu and the anterior two-thirds of the posterior limb contain the pyramidal fibres for the head, arm, trunk, and leg in the order mentioned from before backwards. Behind the pyramidal fibres are in order the fillet, the auditory radiation, the temporo-pontine fibres, and the optic radiation (fig. 27).

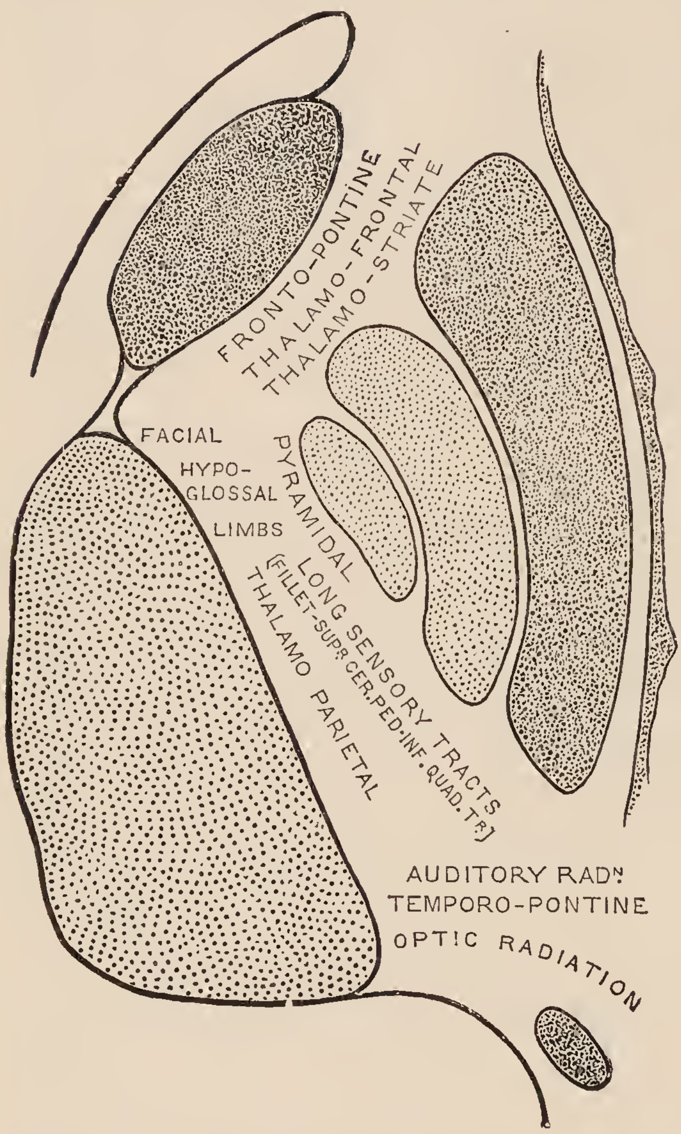


Fig. 27.—Diagrammatic representation of the internal capsule, as seen in horizontal section. (Cunningham.) From Starling's *Principles of Physiology*.

THE PATHS BETWEEN THE CEREBRAL HEMISPHERES AND THE SPINAL CORD.

Afferent impulses enter the spinal cord by the posterior nerve roots. Those for muscle sense and tactile discrimination travel by the posterior column to the nucleus gracilis and nucleus cuneatus in the medulla oblongata. From these nuclei fibres arise and cross to the opposite side, where they enter into the formation of the fillet. The fillet passes through the pons and mid-brain and internal capsule to terminate in the thalamus, from which the impulses are conveyed to the cortex of the cerebral hemisphere by the thalamo-cortical fibres (fig. 28). The paths for tactile localisation, pain, heat, and cold cross in the spinal cord very shortly above the entrance of the posterior roots by which they were conveyed. They travel up by the spino-thalamic tract, or possibly by short segmental tracts, to the medulla oblongata, and there join the fillet, their subsequent course being that just described.

The pyramidal (cerebro-spinal) fibres take origin as the axons of the Betz cells in the motor area, pass through the white matter of the cerebral hemisphere, through the internal capsule, the crusta of the mid-brain, and the pons to become the pyramid of the medulla

oblongata. Most of these fibres cross in the pyramidal decussation to form the crossed pyramidal tract, and terminate by turning into the grey matter of the spinal cord, where they pass their impulses on, probably through an intermediate neuron, to the cells of the anterior horn, the axons of which become the motor fibres of the nerves to the

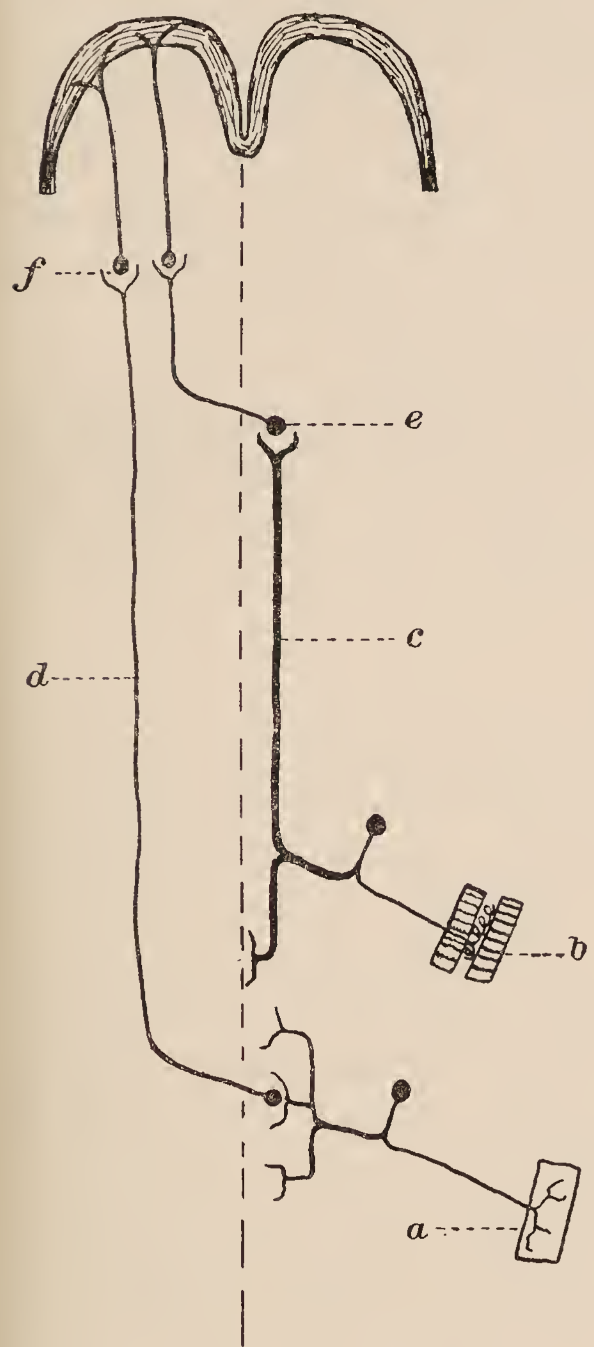


FIG. 28.—Diagram showing paths of sensory impulses.

a, Skin ; *b*, muscle ; *c*, funiculus gracilis ; *d*, spino-thalamic tract ; *e*, nucleus gracilis ; *f*, thalamus.

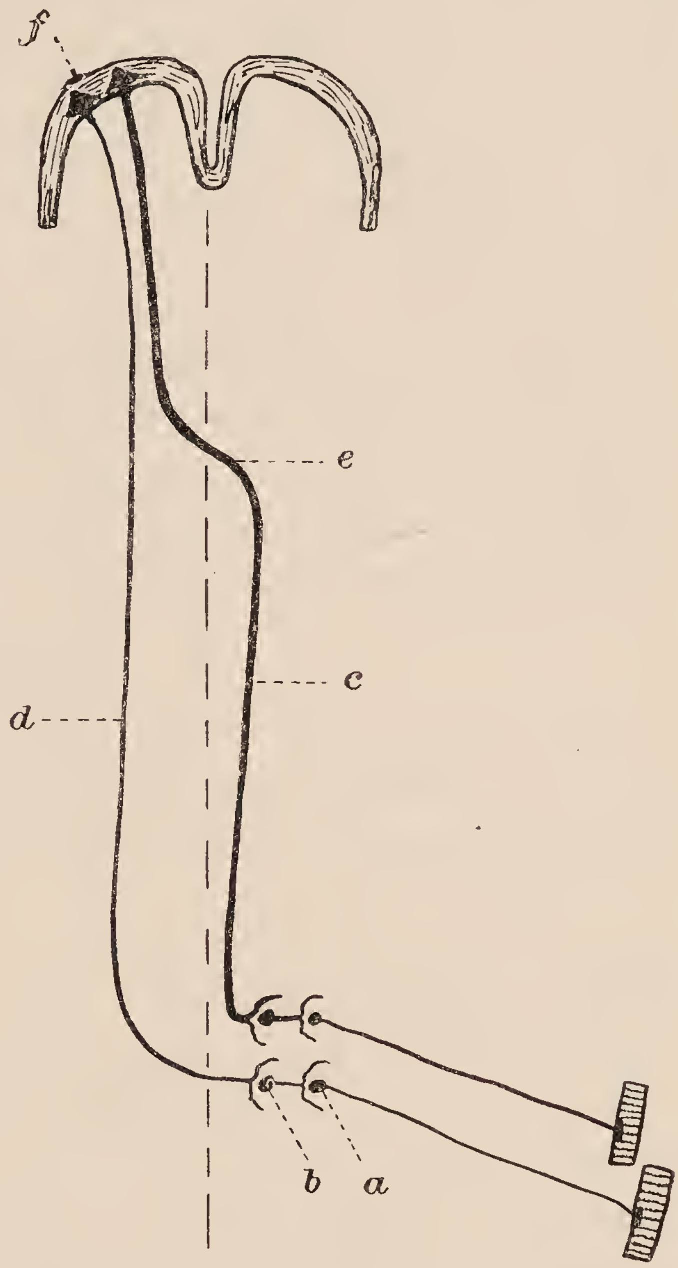


FIG. 29.—Diagram showing the paths for motor impulses.

a, Cell in anterior horn of grey matter ; *b*, cell in posterior horn ; *c*, crossed pyramidal tract ; *d*, direct pyramidal tract ; *e*, decussation of pyramids ; *f*, motor area in cortex.

skeletal muscles (fig. 29). The pyramidal fibres which do not cross in the medulla oblongata form the direct pyramidal tract of the spinal cord, and cross by degrees to the grey matter of the opposite side to come into relation with the cells of the anterior horn. Some of the uncrossed fibres join the crossed pyramidal tract of the same side, and their further course is unknown. Generally speaking, however, the

pyramidal fibres from each cerebral hemisphere convey impulses to the contralateral side of the body.

FATIGUE.

The seat of fatigue in a muscle-nerve preparation is the end-plates. The causation of fatigue, however, in the intact animal is a very complex process, and other factors than the end-plates are concerned, the most important being the central nervous system. Even the fatigue brought about by muscular exercise probably has its origin to a larger extent in the nervous system than in the muscles themselves, the part of the nervous system which becomes fatigued being in all probability the synapses. The changes in the nerve cells which are brought about by prolonged exercise also indicate that fatigue is partly nervous in origin. It must be remembered also that the sense of fatigue does not correspond exactly with the degree of fatigue as measured by the capacity of the muscles to do work; and the effect of psychical influences in lessening or abolishing the sense of fatigue is well known.

SLEEP.

Every active tissue of the body has alternating periods of activity and rest. Thus the ventricles of the heart have a period of contraction of three-tenths of a second followed by a period of relaxation of five-tenths of a second. In the case of the other muscular tissues and of the glands, the periods are longer and are often irregular, but the same general principle holds good. The active phase of the cells in the cerebral cortex which subserve consciousness coincides with the waking period, while the resting phase is the period of sleep. During sleep consciousness is in abeyance and the activity of all the vital processes is lowered; respiration is slower, the heart beats more slowly, glandular secretions are reduced in quantity, metabolic changes generally are diminished, and the temperature falls. Histological observations on the nerve cells in sparrows show that certain spindle-shaped, clear bodies (Nissl spindles) disappear from the cells during the activity of the day and are restored during the night's rest. It may be concluded that katabolic changes exceed anabolic during the waking hours, and that the reverse is the case during sleep.

The cause of sleep has been much discussed, and it is generally agreed that it is associated with a diminished supply of oxygen. It has been shown experimentally that if oxygen is withheld the subject of experiment may become unconscious before he is aware of any unpleasant symptom. The cells of the cerebral cortex are therefore peculiarly susceptible to a deficiency of oxygen. It has been suggested

that these cells accumulate an excess of oxygen during sleep and gradually use it up during the day. However that may be, there is evidence to show that the blood-flow is side-tracked during sleep, so that the brain receives a smaller supply than it does in the waking hours. If a limb be enclosed in a plethysmograph, it is found that the volume of the limb increases during sleep owing to dilatation of the blood-vessels. As a result, the supply of blood to the brain is diminished. Howell suggests that the dilatation of peripheral blood-vessels may be due to fatigue of the vaso-motor centre, but the ultimate cause is still uncertain. Probably the lessened blood supply is secondary to the diminution in functional activity.

THE CEREBRO-SPINAL FLUID.

The cerebro-spinal fluid forms a water cushion by which the brain and spinal cord are protected from jarring shocks during any sudden movement of the body; it may also contain substances which influence the functional activity of the nervous tissues. It occupies the space between the membranes of the brain and spinal cord, and fills the ventricular cavities of the brain and the central canal of the cord. The fluid lying in the ventricular cavities communicates with that which fills the space between the membranes at the foramen of Majendie and at two other foramina, one of which lies at each side of the recess of the fourth ventricle.

The cerebro-spinal fluid resembles lymph, but is much less concentrated than that fluid. It is clear and limpid, and has a specific gravity of about 1007. It contains traces of proteins, and its inorganic constituents correspond with those of blood plasma.

If the dura mater is punctured, the cerebro-spinal fluid escapes from the opening, showing that it is under a certain degree of pressure, which can be measured by inserting a cannula between two vertebræ and connecting it with a manometer. It is found that the pressure corresponds roughly with the venous blood pressure, and that it varies to a slight extent with variations in arterial and venous pressure.

If the cerebro-spinal fluid is allowed to escape, it is rapidly replaced. This is shown in cases where the escape continues for some time, either in conditions experimentally produced in animals, or in such accidental circumstances as fracture of the base of the skull in man. A loss of 100 c.c. or more per hour has been known to continue for weeks in a human being.

The cerebro-spinal fluid is derived from the choroid plexus, and Dixon and Halliburton have recently shown that it is formed by a process of secretion. The normal stimulus to secretion is a hormone

which can be extracted either from the choroid plexus itself or from brain tissue by means of normal saline or other fluids; injection of this extract into the blood stream is followed by an increased flow of cerebro-spinal fluid, which may be collected by means of a cannula. The hormone contained in the extract is not destroyed by boiling and is soluble in alcohol. It is not a protein, but must have a relatively large molecule, since it will not pass through a Chamberland filter.

That the fluid is not formed by filtration is shown by experiments in which a fall of blood pressure is accompanied by an increased production of the fluid. For example, if one vagus nerve is divided and the peripheral portion stimulated, the blood pressure may fall to zero both in the carotid artery and in the cranial veins, while at the same time the pressure of the cerebro-spinal fluid shows a very marked rise. The explanation of this rise is found in the diminished supply of oxygen to the brain and the local accumulation of carbonic acid. The pressure exhibits a considerable rise if the air breathed is either deficient in oxygen or contains an excess of carbonic acid—for example, if it contains 5 per cent. of the latter gas. In this connection it is interesting to notice that the cerebro-spinal fluid may contain in normal circumstances 53 to 61 volumes per cent. of carbonic acid, 40 volumes of which are in firm combination, whereas it only contains 0·1 to 0·3 volume per cent. of oxygen.

The production of the fluid is also increased, but to a less extent, by injections of cholesterol, pilocarpine, or atropine, and by the administration of anæsthetics. It is diminished by increased ventilation of the lungs, or by an increased amount of oxygen in the air breathed. If there is a sufficient supply of oxygenated blood, the pressure of the cerebro-spinal fluid varies with the blood pressure; it rises therefore with the administration of adrenalin, though this substance has no effect on the amount of the secretion.

Changes in the pressure of the cerebro-spinal fluid affect the respiratory, vaso-motor, and cardio-inhibitory centres, a moderate rise of pressure having a stimulating effect and a greater rise paralysing the centres. When the pressure is raised to 300–400 mm. Hg, respiration ceases in a few seconds, a little later the cardio-inhibitory centre is paralysed, and later still the vaso-motor centre. When the pressure is relieved, the vaso-motor centre recovers first and the respiratory centre last.

SECTION IX.

THE AUTONOMIC SYSTEM.

In contradistinction to skeletal muscle, the unstriped muscle which is found in the walls of the arterioles, digestive tract, uterus, bladder, and elsewhere, is not under the control of the will, though its contraction is regulated by impulses arising in the central nervous system. The nerves which supply these structures, and also those to the secretory glands, form the autonomic system.

This consists of (1) branches of some of the cranial nerves, including the vagus and the chorda tympani, and of fibres issuing from the anterior roots of the second and third sacral nerves and known as the nervi erigentes; and (2) the sympathetic system, the pre-ganglionic fibres of which leave the spinal cord in the anterior roots of all the spinal nerves from the first thoracic to the fourth lumbar.

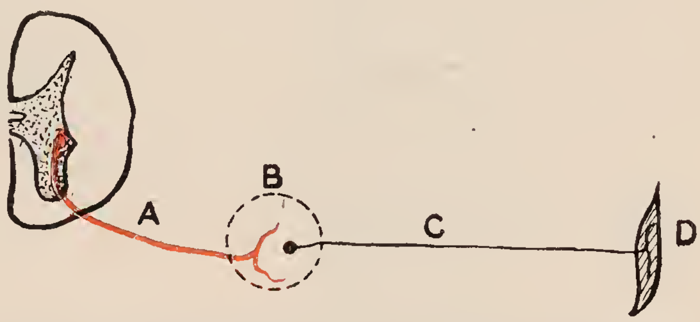


FIG. 30.—Diagram to show relation between pre-ganglionic and post-ganglionic fibres.

E, Spinal cord; A, pre-ganglionic fibre; B, cell station; C, post-ganglionic fibre; D, unstriped muscle-fibre.

The *pre-ganglionic* nerve fibres are medullated and small, varying in diameter from 2 to 4μ; they are not distributed directly to the tissue which they supply, but every fibre ends round a nerve cell which lies in a sympathetic or other ganglion; from this cell a fresh fibre, which is called *post-ganglionic* and is usually non-medullated, starts and passes to the peripheral tissue (fig. 30). The point at which the pre-ganglionic fibre comes into contact with the dendrites of a ganglion cell forms a cell station or synapse; and the nervous impulse, issuing from the central nervous system along a pre-ganglionic fibre, normally passes across the synapse to the ganglion cell and then along the post-ganglionic fibre to the peripheral tissue.

Although the entire autonomic system is built up on this general plan, namely (1) pre-ganglionic fibre, (2) cell station, (3) post-ganglionic fibre, and (4) nerve ending, the actual anatomical distribution of the fibres and the situation of the cell stations are very varied. The fibres issuing from the brain and from the sacral region of the spinal cord have their cell station close to or actually within the organ which they supply. The fibres of the sympathetic system take a different course. Lying along each side of the vertebral column is a chain of ganglia which forms the lateral sympathetic chain (fig. 31). As a rule there is one

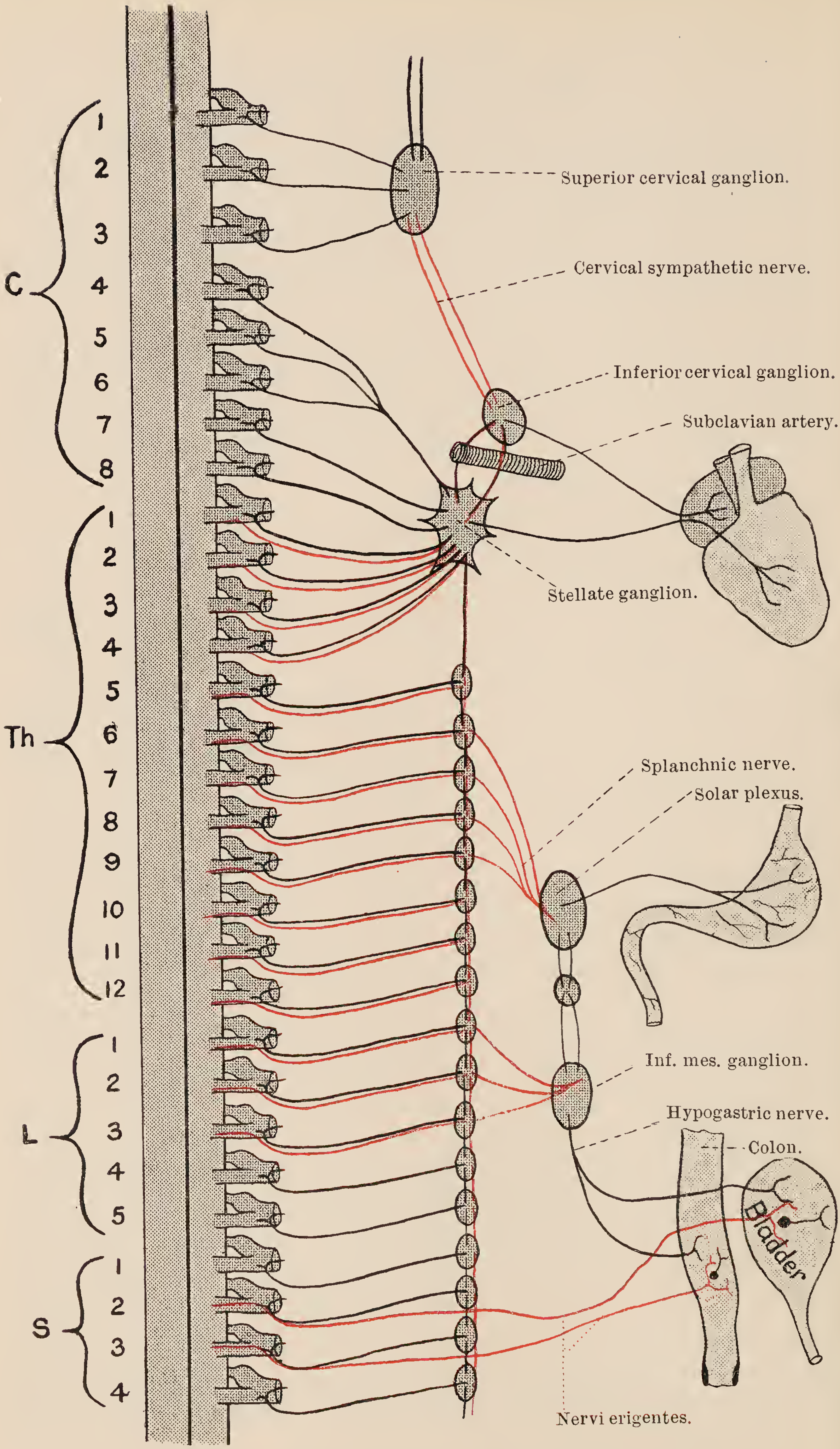


FIG. 31.—Diagram of autonomic nervous system (excluding cranial nerves). Pre-ganglionic fibres, red; post-ganglionic, black.

ganglion corresponding with each spinal nerve root, but the upper four thoracic ganglia are fused into one larger mass, the stellate ganglion. In the cervical region there are in most animals only two ganglia, inferior and superior, united by the cervical sympathetic nerve. The pre-ganglionic sympathetic fibres leave the anterior root in the thoracic and upper lumbar region as a series of small nerves, the white *rami communicantes*, each of which enters the corresponding ganglion of the lateral sympathetic chain. Some of these fibres, including those which carry impulses to the blood-vessels of the skeletal muscles and skin, and to the hairs and sweat glands, have their cell stations in one or other of the sympathetic ganglia; and the post-ganglionic fibres form small nerves (called grey rami), one of which joins each of the spinal nerves. The sympathetic fibres which supply the blood-vessels and other structures of the head leave the spinal cord by the first to the fourth or fifth thoracic white rami, and pass through the stellate ganglion up the cervical sympathetic nerve to the superior cervical ganglion; their cell stations lie in this ganglion, and the post-ganglionic fibres leaving it are distributed to the blood-vessels, salivary glands, and other structures in the head.

The fibres which supply the heart leave the spinal cord by the second and third thoracic white rami, and have their cell station in the stellate ganglion, from which post-ganglionic fibres pass directly to the heart.

The fibres which are distributed to the abdominal viscera issue from the spinal cord by the lower six thoracic and the first lumbar white rami, pass through the corresponding ganglia of the sympathetic chain without forming a cell station, and are gathered up into two large nerves, one on each side, known as the splanchnic nerves. These enter two large ganglia, the semilunar ganglia or solar plexus, in which lie the cell stations of almost all the fibres running in the splanchnic nerves. Some of the post-ganglionic fibres leaving these ganglia are distributed to the blood-vessels of the abdominal viscera, while others supply the walls of the digestive tract. Fibres also pass along the white rami of the upper lumbar nerves to the inferior mesenteric ganglia, from which post-ganglionic fibres run in the hypogastric nerves to be distributed to the pelvic organs.

Nicotine, in small doses, first stimulates and then paralyses the synapses between the pre-ganglionic fibres and the nerve cells in the autonomic ganglia, thereby preventing the passage of an impulse through the cell stations; it does not affect the nerve fibres themselves. By means of nicotine, the course taken by the autonomic fibres and the situation of their cell stations have been determined. The drug is painted on a ganglion, and the fibres passing to and from it are stimulated; if stimulation of the fibres passing to the ganglion is

ineffective, it is clear that they have their cell station in that ganglion. For example, when nicotine has been painted on the superior cervical ganglion, stimulation of the cervical sympathetic nerve produces none of the effects which are observed in the normal animal, whereas stimulation of the fibres leaving the ganglion produces the same effect after the application of nicotine as before. The experiment shows that the fibres running in the cervical sympathetic nerve have their cell stations in the superior cervical ganglion.

The fibres of the autonomic system supply not only the blood-vessels but other structures, including the walls of the digestive tract and pelvic viscera, the heart, sweat glands, and hairs. Their course and function will be fully considered in subsequent chapters, but may be summarised here.

I. *Cranial autonomic fibres.*

Third nerve.—The autonomic fibres pass to the ciliary ganglion, where they have their cell station, and supply the intrinsic muscles of the eye.

Seventh and ninth nerves.—The autonomic fibres supply vaso-dilator fibres to the tongue, and secretory fibres to the salivary glands.

The vagus sends inhibitory fibres to the heart, motor fibres to the œsophagus, stomach, small intestine, and bronchioles, and secretory fibres to the stomach and pancreas; the cell stations probably lie in the walls of the structures supplied by the different fibres.

II. *Sacral autonomic fibres.*—These supply dilator fibres to the blood-vessels of the penis, and motor fibres to the muscles of the rectum and bladder.

III. *Sympathetic fibres.*

(1) The fibres to the head leave the spinal cord in the first five thoracic white rami, and run in the cervical sympathetic nerve; this contains vaso-constrictor fibres for the blood-vessels, secretory fibres for the salivary glands, and dilator fibres for the pupil.

(2) The fibres to the heart have their cell station in the stellate ganglia, and convey accelerator impulses.

(3) The fibres to the abdominal viscera leave the spinal cord in the lower six thoracic and the first lumbar white rami. Most of them have their cell stations in the semi-lunar and superior mesenteric ganglia, from which they are distributed. They convey constrictor impulses to the blood-vessels of the stomach, small intestine, kidneys, and spleen, inhibitory impulses to the muscular walls of the stomach and small intestine, and motor impulses to the ileo-colic sphincter.

(4) The pelvic viscera are supplied from the white rami of the last thoracic and upper lumbar nerves, the cell station being in the

inferior mesenteric ganglia. The nerves convey constrictor impulses to the blood-vessels of the pelvic organs and inhibitory impulses to the muscular coats of the colon, uterus, and bladder.

(5) Fibres are also contained in all the white rami which have their cell station in the lateral chain of ganglia, the post-ganglionic fibres passing usually, but not always, into the corresponding spinal nerve to be distributed to the blood-vessels of the muscles and skin, and to the sweat glands and hairs in the area supplied by that nerve.

It will be noticed that many organs are supplied by two sets of fibres having opposite functions.

FUNCTIONS OF THE GANGLIA.

The cells of the ganglia serve as distributing centres, and each pre-ganglionic fibre arborises round a number of cells, so that the post-

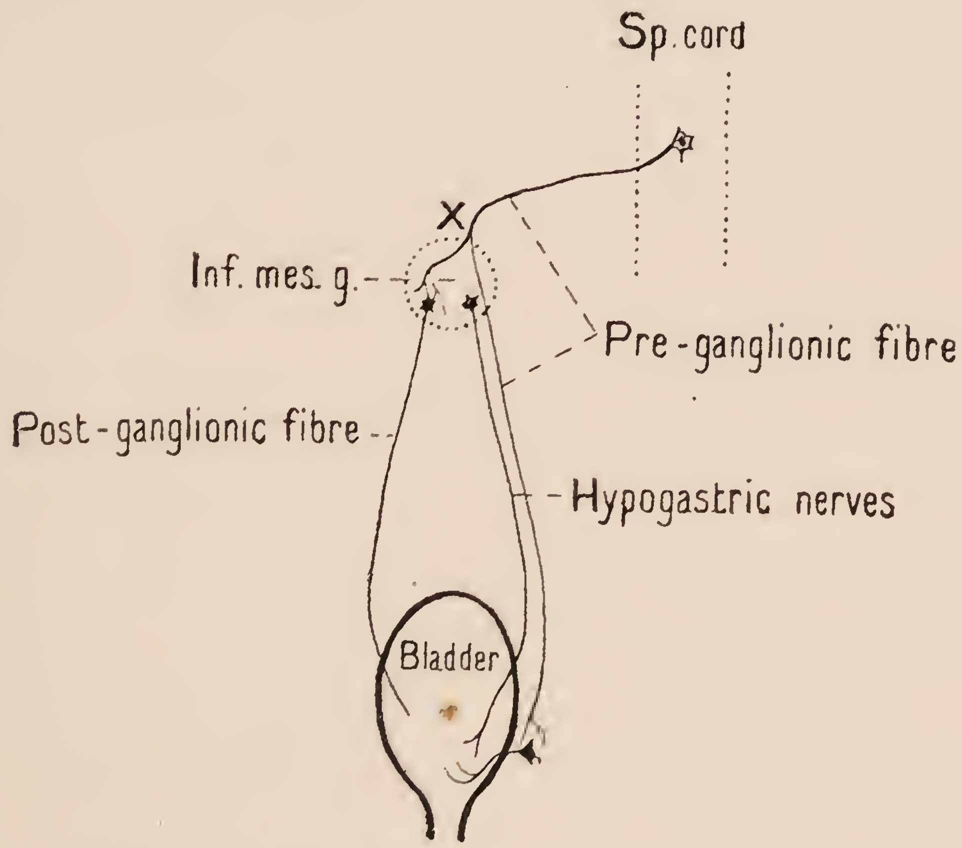


FIG. 32.—Diagram showing the structures concerned in the "axon-reflex" referred to in the text. (Starling's *Principles of Physiology.*)

ganglionic fibres are much more numerous than the pre-ganglionic fibres.

At one time various reflex actions were attributed to the sympathetic ganglia, but these have been proved to be not true reflexes, but pseudo- or axon-reflexes. For example, when the nerves connected with the inferior mesenteric ganglion are divided, with the exception of the right hypogastric nerve to the bladder, stimulation of the central end of the left hypogastric nerve causes contraction of the right half of the bladder. This is due to the fact that some of the fibres leaving the

spinal cord branch in the ganglion, one branch passing down the left nerve, the other entering into the formation of a cell station connected with the right hypogastric nerve (fig. 32). Stimulation of the central end of the left nerve causes an impulse to pass up to the point of junction of the two branches, and then down the other branch through the cell station to the bladder. This effect is called an *axon reflex*, and depends upon the fact that nerve fibres may conduct impulses in either direction.

The autonomic system also contains afferent fibres, though these are less numerous than the efferent fibres; in the splanchnic and hypogastric nerves about one-tenth of the fibres are afferent. The stimulation of these fibres by abnormal processes in the abdominal organs may give rise to pain. The pain is usually referred, however, not to the organ itself, but to the surface of the body; for instance, afferent impulses from the stomach may give rise to pain which is referred to an area of skin at the lower border of the ribs, and this area may actually be tender to touch. The position of the referred pain and of tender cutaneous areas has proved of value in man as a means of localising disease of the internal organs.

CHAPTER VI.

THE ORGANS OF SENSE.

SECTION I.

The organs of sense, with their nerves, form the medium by which afferent impressions are conveyed to the cortex of the cerebral hemispheres. If the sensory mechanism is concerned with impulses excited by stimuli from without, it is described as exteroceptive; if the stimuli arise in the viscera, the mechanism is called enteroceptive; if they arise in the muscles or sense organs affected by the position of the body, the mechanism is proprioceptive. Thus the exteroceptive system includes the structures which have to do with sensations of pressure, taste, smell, sight, and hearing; the enteroceptive system includes the mechanisms for hunger and thirst; and the proprioceptive system has to do with sensations of position of the head and limbs and of the degree of muscular contraction.

The structures concerned in the production of sensation are: (1) an end-organ, (2) a chain of neurons which transmits the impulse, and (3) the sensory, psychic, and association areas in the cortex to which the impulse is transmitted. The end-organs for each sense are structurally adapted to receive the stimulus for that particular sense, this being known as the adequate stimulus. Thus the rods and cones of the retina are stimulated by waves of light, but not by waves of sound, while the hair cells in the organ of Corti are excited by sound waves but not by those of light. The nerve fibres which transmit the impulses, on the other hand, appear to be able to transmit any variety of stimulus, and they all give the same type of electrical variation when stimulated by an electric current.

Although the various sense organs differ widely in structure, certain general principles can be formulated which are applicable to them all.

(1) Stimulation of the end-organs of any particular sense gives rise to the sensation peculiar to that sense, and to that sensation only;

in other words, each sense has its own specific quality or *modality*. This characteristic was stated by Müller in the form of a law, which he called the "law of specific nerve energy." It is better, however, in view of the restricted modern use of the word energy, to speak of the law of specific irritability. The quality of the sensation aroused might be determined by the nature of the receptive end organ, by the conducting apparatus, or by the area of the cortex to which the impulse is transmitted. Direct stimulation of the central portion of a divided sensory nerve gives rise to the specific sensation, so that the modality is not determined by the end-organ. For example, pressure on the ulnar nerve trunk excites a pricking sensation referred to the distribution of the nerve, and section of the optic nerve in a conscious patient is accompanied by the sensation of flashes of light. Again, there is no reason to believe that the conducting nerve fibres have any more influence on the nature of the impulse they convey than an electric wire has in determining the nature of a telegraphic message. It is, therefore, in the cortex of the cerebral hemisphere that the explanation of the specific character of the sensation is to be sought, and this conclusion is supported by the fact that sensations may be aroused in the absence of any stimulation of the end-organs, *e.g.* in dreams or hallucinations.

(2) In the case of each sense a certain minimal strength of stimulus, known as *the threshold stimulus*, is necessary to evoke a sensation. The exact strength of the threshold stimulus for any particular sense varies in different individuals, and also in the same individual at different times. A succession of subliminal stimuli, that is, of stimuli each of which is below the threshold value, may excite a sensation by a summation effect, just as the summation of subminimal stimuli may excite a reflex action. The threshold value will vary with the condition of the sense organ. For example, the mechanism may be fatigued, and will then be less responsive to stimulation. This is well illustrated in the case of smell. The air of a closed room, which is occupied, becomes disagreeable, but the occupants of the room do not notice the unpleasant smell, which is at once apparent to anyone coming in from the outer air. The threshold value also varies with the state of adaptation of the sense organ. Thus an eye which has been exposed to light is said to be light-adapted, while one that has been in darkness for a time is dark-adapted. The threshold value of the light stimulus for the dark-adapted eye is much lower than, actually about one-fiftieth of, that required to produce a sensation in the light-adapted eye.

(3) The increase of stimulus necessary to cause a difference in the

degree of sensation bears a constant proportion to the strength of the original stimulus. If the eye is being stimulated by the light of one hundred candles, the extra stimulation required to produce the sensation of more light can be derived from one more candle. If, however, the original stimulus came from one thousand candles, then ten more candles would be required for a difference to be detected.

Similarly, if a weight of 30 grams is held in the hand, one more gram must be added to excite a sensation of increased weight, and a smaller increase would not be noticed. If the original weight is 60 grams, 2 grams must be added for the difference to be perceptible. So also in the case of sound, the stimulus must be increased by one-seventh to lead to the perception of increased sound volume. In all cases this law, which is known as Weber's law, only holds good within certain definite limits, the limits for the pressure sense as tested by weights lying between 50 and 1000 grams.

CUTANEOUS SENSATIONS.

The sensations aroused by the application of different varieties of stimuli to the skin are those of pressure, including tactile localisation and tactile discrimination, heat, cold, and pain. These various sensations are independent and do not result from different forms of stimulation applied to the same set of nerve endings. The evidence that tactile localisation, tactile discrimination, heat, cold, and pain are distinct senses is (1) histological, (2) the existence of independent spots in the skin, stimulation of each of which gives rise to one variety of sensation only, and (3) the fact that interference with the conducting paths may result in blocking of one set of impulses, for example, those giving rise to pain, while the other senses are unaffected.

Histological. The End-organs in the Skin.—The peripheral fibre from a cell in the posterior root ganglion or the homologous ganglion on a cerebral nerve terminates in the skin in various ways. The termination may be free, or it may be protected. *Free nerve endings* are found in the anterior epithelium of the cornea; the axis cylinder of the nerve fibre loses its myelin sheath at the periphery of the cornea, and, after forming a plexus in the corneal substance, the fibre terminates between the epithelial cells in the form of fine varicose fibrils. Similar terminations are found in the epidermis, and fibrillar nerve endings occur also around the hair follicles. The *protected nerve endings* are all formed on the same general plan. There is a central soft core surrounded by a variable amount of fibrous tissue, arranged sometimes irregularly, and sometimes, as in the Pacinian corpuscles, in laminæ. The nerve fibre loses its myelin sheath and runs into the core of the

end-organ, where it ends in one or more knob-like extremities. Such endings are the *end-bulbs* found in the conjunctiva, penis, clitoris, and in the synovial membrane of some joints: the *touch corpuscles of Meissner* in the connective-tissue papillæ of those parts of the skin which are most sensitive to pressure, that is, in the hand and front of the forearm, the lips, the foot, and the mammary papilla: the *Pacinian corpuscles* found in the subcutaneous tissue of the hand, foot, and genital organs, and in the mesentery and some organs, such as the pancreas: the *corpuscles of Golgi and Mazzoni* and the *corpuscles of Ruffini*, found in the subcutaneous tissue of the fingers.

The Sensory Spots in the Skin.—If a cooled metal point is drawn gently along the skin of the forearm or back of the hand, a sensation of cold is produced at certain definite spots, which may be marked out with coloured ink. If the point is heated and the experiment repeated, it is found that other spots, quite distinct from those for cold, respond and give the sensation of heat. Similarly, by using the prick of a needle as the stimulus, another series of spots may be marked out which give rise to pain. Lastly, by testing the pressure sense with a bristle a fourth set of spots may be located. The most numerous spots in the skin are those for pain; next in order are the pressure spots, those for cold being less numerous, and the heat spots fewest of all. The specific character of the different nerve endings is confirmed by the effect of other stimuli. The application of menthol to the skin, for example, stimulates especially the nerve endings for cold and gives rise to a sensation of coolness. If the arm be held in a jar of carbonic acid gas, on the other hand, there is a sensation of warmth, the nerve endings for heat being especially affected. Electrical stimulation of the various spots excites a specific sensation, namely, warmth in a heat spot, pain in a pain spot, and so on. Additional evidence as to the independence of the sensations is derived from the effect of cocaine on the surface of the eyeball. Under normal conditions suitable stimulation of the conjunctiva excites the sensations of heat, cold, or pain, whereas stimulation of the cornea gives rise to the sensation of pain only. The application of cocaine to the eye paralyses the nerve endings for pain, but does not affect those for heat or cold.

The Conduction of Cutaneous Impulses.—The nerve fibres which convey the cutaneous impulses are bound together in common trunks. Prolonged pressure on these trunks acts as a block to the conduction of impulses, and occasionally cases occur in which, by the pressure of a bony outgrowth or otherwise, a partial block is produced, whereby the pressure and temperature senses are lost, while that of pain is retained, or *vice versa*. A similar partial block occurs at times in the disease

known as syringomyelia, in which there is pressure on the conducting paths in the spinal cord owing to distension of the central canal. In these cases also there may be loss, for example, of the senses of pain and temperature, while that of pressure is retained.

The cutaneous senses are therefore independent and are subserved by different nerve fibres, but the further question as to whether each sense has a specific nerve ending cannot be so decisively answered. Special functions can, however, be ascribed to some of the nerve endings in the skin with a reasonable degree of probability.

The fact that any stimulus applied to the cornea gives rise to pain indicates that interepithelial fibrillar nerve endings are associated with the pain sense. The skin areas most sensitive to pressure are those, like the palmar surface of the fingers, where the touch corpuscles of Meissner are most abundant. Where hair is present the pressure spots immediately surround the point of emergence of the hair. It may therefore be concluded that the touch corpuscles in hairless regions and the fibrillar nerve endings around the hair follicles are the peripheral terminations of the pressure sense fibres. Finally, the position of the Pacinian corpuscles and of those of Golgi and Mazzoni and of Ruffini makes it clear that these structures can only be affected by deep pressure.

THE DISTRIBUTION OF THE CUTANEOUS SENSORY NERVE ENDINGS.

Reference has already been made to the fact that the cornea is richly supplied with nerves for pain, and that the skin of the palmar surface of the fingers is markedly endowed with the pressure sense. The distribution of the various sensory nerves is therefore unequal, and investigations have been made, especially in connection with the pressure sense, to determine (1) the degree of pressure which can be detected at different parts of the skin surface, and (2) the relative acuteness in different areas of tactile discrimination, that is, of the power of appreciating two separate pressure stimuli applied simultaneously.

(1) Von Frey's method of estimating the degree of pressure on the skin which can be appreciated is to use hairs of different thickness, the pressure required to cause each to bend being known. In this way he found that the skin of the nose and lips and the mucous membrane of the tongue are most sensitive to pressure, while the skin of the region of the loins has a very low degree of sensitivity. The minimum stimulus which could be detected in different skin areas is shown in the following table:—

Area.	Grams per sq. mm.
Tongue and nose	2
Lips	2·5
Finger-tip and forehead	3
Palm, arm, thigh	7
Forearm	8
Back of hand	12
Abdomen, outside of thigh	26
Back of forearm	33
Loins	48

(2) Tactile discrimination is measured by means of the æsthesiometer, an instrument somewhat resembling a pair of compasses, one limb of which can be moved along a scale on which the distance between the two points can be read off. When the two points, armed with small pieces of cork, are applied to the skin a sufficient distance apart, the resulting sensation is of two separate stimuli. When the two points are approximated, the degree of approximation varying for different parts of the skin surface, the double stimulus is productive of a single sensation. The minimal distance apart at which the points give rise to separate sensations is shown in the following table:—

Skin region.	Distance in mm.
Tip of tongue	1·1
Volar surface of finger-tip	2·3
Palm of hand	11·3
Back of hand	31·6
Middle of back, upper arm, thigh	67·1

These figures have no reference to the distances which separate the actual pressure spots, but include on an average about ten such spots in each case between the limbs of the æsthesiometer.

LOCAL SIGN.

Just as a localised stimulus of a definite kind applied to the skin invariably evokes the same reflex, so also in a conscious individual a stimulus applied to a particular skin area is referred to the stimulated spot. There must therefore be a specific quality in the impulse conveyed to the association centres according to the skin area in which it originates, and this quality is called "local sign." It has been supposed by some authorities that local sign is due to a recognition of the muscular reflexes which are or may be evoked as a result of the stimulus, but it is more probable that it is developed as the result of experience. If the index and middle fingers be crossed and a pea be

placed between them in this position (Aristotle's experiment), the sensation produced will be of two peas, because the individual has no previous experience of a single stimulus applied in this way.

PROTOPATHIC AND EPICRITIC SENSIBILITY.

The investigations of Head have made it possible to subdivide cutaneous sensations into two main groups, protopathic and epicritic. This classification is based upon a study of the order of return of the cutaneous sensations during regeneration after division of nerves. Head observed the recovery of sensation in patients in whom nerves had been accidentally divided, and also had one of his own cutaneous nerves divided in order to study the matter subjectively. He found that after section of a cutaneous nerve all cutaneous sensations were lost, but that there remained the sensations of deep pressure and of pain due to deep pressure, which depend on stimulation of the afferent fibres in the muscles. During regeneration of the divided nerve, the first sensations to return are those of pain, of heat for temperatures above 38° C., and of cold for temperatures below 24° C. These are the protopathic sensations, and they return from seven to twenty-six weeks after the division of the nerve. Tactile localisation and discrimination, the accurate localisation of pain in the skin, and the sense of heat and cold between 37° C. and 25° C., are recovered in from one to two years after the nerve section, and constitute the epicritic sensations.

Protopathic sensations are "affective" in character, the sensation being intense, prolonged, and usually disagreeable; they are obviously associated with the defensive mechanism of the body. The seat of the protopathic sensations is believed to be located in the thalamus. Epicritic sensation, on the other hand, is on a higher plane, and is essential for the development of manual dexterity. It may be looked upon as the latest and highest evolution of the tactile sensory mechanism, and the seat of sensation is in the cortex of the cerebral hemispheres.

SECTION II.

THE SENSES OF TASTE AND SMELL.

The sense of taste is localised in the mucous membrane of the mouth and fauces, especially in that covering the tongue, and the end-organs concerned are widely distributed in the mucous membrane. The principal distribution of the nerves of taste, however, is in connection with the vallate papillæ which are found at the base of the tongue. Structures called taste bulbs lie in the stratified squamous epithelium

on both sides of the vallum which surrounds each papilla. A taste bulb is an oval body bounded externally by spindle-shaped cells, and containing in its interior other cells which are fusiform; each of the latter terminates at its peripheral extremity by a hair-like process, which projects into the vallum through an aperture called the gustatory pore. The terminations of the fibres of the nerves of taste penetrate the other pole of the taste bulb, and end by arborisation round the fusiform cells, which are the end-organs for the sense of taste. Serous glands lie in the connective tissue subjacent to the vallate papillæ, and their ducts open into the lower part of each vallum.

The substances which act as stimuli for the sense of taste must be in solution. Ordinary foodstuffs possess both taste and flavour, the appreciation of the latter depending on the sense of smell, so that, if the nose be firmly held so as to prevent air currents reaching the olfactory membrane while food is in the mouth, flavours are not appreciated. There are only four true taste sensations—sweet, bitter, salt, and sour. Any other sensation excited in the mouth, for example, astringency, is due to stimulation of the nerves of common sensibility.

As in the case of the skin, so in the case of taste, different nerves are concerned in the different sensations. This is shown (1) by the fact that some areas of the tongue are more sensitive than others to the different sensations, and (2) by the effect of drugs. Thus (1) the tip of the tongue is most sensitive to substances giving rise to the sensation of sweetness, the back to those which arouse a bitter sensation, the sides and upper surface to appreciation of sourness, while a salt taste may be excited over the surface generally. There are, moreover, substances which give different taste sensations according to the part of the tongue on which they are placed. Parabrom-benzoic sulphinid, for example, excites a sweet sensation if placed on the tip of the tongue, but only a bitter sensation if placed on the posterior part. Further, the individual papillæ have been tested, with the result that some are found to be more sensitive to substances which give rise to a sweet sensation, others to those which excite the other taste qualities, while most are sensitive to more than one quality. (2) Further evidence for the existence of specific nerves for the various taste sensations is derived from the effect of drugs. Cocaine applied to the papillæ has no effect on the production of salt sensations, but it abolishes the other three qualities in a definite order, bitter being the first and sour the last to disappear. Gymnenic acid, from the leaves of *Gymnena sylvestre*, on the other hand, abolishes only the production of sweet and bitter sensations, the former going first.

The nerves of taste are the chorda tympani to the anterior two-

thirds and the glossopharyngeal to the posterior third of the tongue. The taste fibres have their central termination in each case in the column of grey matter which forms the sensory nucleus of the fifth nerve, the nervus intermedius and the glossopharyngeal nerve.

The Sense of Smell.—The end-organs for the sense of smell are limited in their distribution to the upper part of the nasal cavities. The membrane lining this region is yellow in colour, and consists of a characteristic epithelium lying on a connective-tissue layer. The epithelial layer is formed of a superficial layer of columnar, supporting cells and several layers of nerve cells; the latter are elongated in shape, and each possesses a nucleus. The prolongation of the cell peripheral to the nucleus lies between the columnar cells, and terminates at the surface in six to eight hair-like processes; the central prolongation is continued as a non-medullated nerve fibre to the olfactory lobe, where it arborises in the manner already described (p. 92). The connective-tissue layer contains small alveolar glands, known as Bowman's glands, the secretion of which moistens the surface of the membrane.

The adequate stimulus for the sense of smell must be in the gaseous form, or in the condition of excessively minute particles. The gases or particles are conveyed to the lower or respiratory portion of the nasal cavities by the air currents due to the respiratory movements. From the respiratory passage the gases reach the olfactory region by diffusion. No satisfactory classification of odours has been arrived at, and it is usual to describe them as pleasant or unpleasant. Other sensations excited in the nasal mucous membrane, such as the irritation produced by ammonia, are due to stimulation of the endings of the fifth nerve.

The chief characteristics of the sense of smell are (1) its extreme delicacy, and (2) the ease with which it may be fatigued. (1) The delicacy of the sense of smell is indicated by the dilution of a substance which can still be perceived. Musk can be detected in a dilution in air of one in eight millions; mercaptan in a dilution of one in twenty-five billions. (2) The fatiguability of the olfactory sense is shown by the insensibility of a person sitting in a closed room to the fact that the air has become vitiated, and also by absence of sensation from a particular perfume after it has been inhaled for a short time.

Certain odours are antagonistic, that is, one will neutralise the effect of another. Thus the odour of iodoform is annulled by mixing it with balsam of Peru, and carbolic acid neutralises to some extent the odour of putrefaction.

The estimation of the threshold stimulus for the sense of smell is made by means of the olfactometer of Zwaardemaker. This instrument consists of a porous cylinder which is impregnated with the odorous

substance. A tube is inserted into the cylinder for varying distances, so that a greater or less part of the cylinder is exposed to the air which passes through the tube. The end of the tube outside the cylinder is placed in a nostril, and the smallest amount of exposed cylinder surface which will give a sensation indicates the threshold stimulus for the substance tested.

The olfactory sense is developed to a varying extent in different animals. Generally speaking, it is present to a greater degree in many of the lower animals than in man; in the dog, for example, it is highly developed.

SECTION III.

THE SENSE OF SIGHT.

The end-organs of the sense of sight are situated in the eyeball, which is protected from injury by its situation in the orbital cavity and also by the eyelids. The surface of the eyeball is kept moist by the tears, which are secreted by the lachrymal gland. Loss of moisture occurs through evaporation from the surface of the eyeball, and superfluous tears are drained away through the *puncta lachrymalia* at the inner end of the eyelids into the lachrymal sac, and thence by the nasal duct into the nasal cavity. The lachrymal secretion is slightly alkaline and contains sodium chloride.

THE EYEBALL.

The eyeball consists of three coats surrounding the transparent media which constitute the dioptric apparatus. It is covered in front by the conjunctiva, a connective-tissue membrane with a superficial layer of stratified squamous epithelium. The conjunctiva is reflected over the posterior surfaces of the eyelids, and is represented on the cornea only by the layer of stratified epithelium. The outer coat of the eyeball consists of the sclera and cornea. The *sclera* forms five-sixths of the coat, and is protective in function. It is opaque, and is made up of dense fibrous tissue with some elastic fibres and flattened cells, some of which are pigmented. The *cornea* forms one-sixth of the outer coat, and has a somewhat greater convexity than the sclera. It is transparent, and is made up of parallel lamellæ of white fibrous tissue with spaces between, in which lie flattened branched cells, the corneal corpuscles. It is covered in front by stratified squamous epithelium, which rests on a homogeneous-looking membrane composed of closely woven fibrils, and known as the anterior elastic lamina. The posterior surface of the cornea is covered by a single layer of flattened

cells, resting on an elastic, homogeneous membrane, called the posterior elastic lamina. In the inner part of the sclera, close to its junction with the cornea, is a vein, the canal of Schlemm (*sinus venosus scleræ*), which encircles this part of the eyeball. Behind the sinus is a projecting ridge of the sclera, the scleral spur, which forms the point of origin of the radial fibres of the ciliary muscle. At the margin of the cornea the posterior lamina breaks up into trabeculæ, some of which are attached to the anterior surface of the scleral spur, while the others form the *ligamentum pectinatum iridis*, which is continuous with the substance of the iris. The angle between cornea and iris is known as the filtration angle, because here the aqueous humor drains between the fibres of the ligamentum pectinatum iridis into the canal of Schlemm.

The middle coat consists of the choroid, ciliary processes, and iris, together forming the vascular tunic of the eyeball. The *choroid* is separated from the sclera by a lymph space, which, however, is traversed by strands of non-vascular fibrous tissue, constituting the *lamina suprachoroidea*, and forming the outer layer of the choroid itself. Internal to the lamina suprachoroidea is a layer containing the larger blood-vessels, and internal to that is another layer, the chorio-capillaris, which contains a network of capillaries; the capillary layer is bounded internally by a structureless membrane, the *lamina basalis*. Scattered throughout the choroidal tissue are numerous pigment cells.

The choroid lines the sclera to within a short distance of the sclero-corneal junction, and is continued forward from that point as the *ciliary processes*, about seventy in number, which from behind appear as a circle of radially arranged vascular projections. The posterior surface of the ciliary processes is covered by a double layer of cubical pigment cells, forming the forward prolongation of the retina, and called the *pars ciliaris retinæ*. The substance of the ciliary processes consists of connective tissue with pigment cells and blood-vessels, together with the ciliary muscle. The latter is composed of smooth muscle fibres, and consists of a radial and a circular portion. The radial fibres arise from the scleral spur and pass backwards to be inserted into the ciliary processes and choroid; the circular fibres form a bundle which lies internally to the radial portion.

The *iris* is continued forward from the ciliary processes and is incomplete in front, leaving a circular aperture, the pupil. The iris is composed of connective tissue, with a variable number of pigment cells and numerous blood-vessels. In dark eyes the pigment cells are numerous; in blue eyes they are fewer in number. The fibres of the ligamentum pectinatum iridis connect the iris with the posterior lamina

of the cornea. The anterior surface of the iris is covered by a single layer of flattened cells, continuous over the ligamentum pectinatum with that of the posterior surface of the cornea. The posterior surface is covered by a double layer of cubical pigment cells continuous with the pars ciliaris retinæ. A ring of circularly arranged smooth muscle fibres lies close to the margin of the pupil, forming the sphincter pupillæ, and radially arranged smooth muscle fibres, the dilator pupillæ, lie close to the posterior surface of the iris.

The internal coat of the eye consists of the *retina*, a delicate, semi-transparent membrane lining the posterior three-fourths of the eyeball, and ending abruptly just behind the ciliary processes in a jagged margin, the *ora serrata*. The retina consists from without inwards of the following layers (fig. 33):—

1. The layer of pigment cells.
2. The layer of rods and cones.
3. The outer nuclear layer.
4. The outer molecular layer (outer plexiform layer).
5. The inner nuclear layer.
6. The inner molecular layer (inner plexiform layer).
7. The layer of ganglionic nerve cells.
8. The layer of nerve fibres (stratum opticum).

The structures forming these layers are supported by the fibres of Müller, which extend from the level of the bases of the rods and cones to the inner surface of the retina. The ends of Müller's fibres are expanded and fused together to form the outer and inner limiting membranes, the former lying between the layer of rods and cones and the outer nuclear layer, and the latter bounding the retina internally. Each fibre has a nucleus at the level of the inner nuclear layer.

(1) The cells of the pigment layer are hexagonal on surface view, and when seen from the side they exhibit an outer non-pigmented portion containing a nucleus, and an inner pigmented part from which delicate processes run between the rods and cones.

(2) and (3) The layer of rods and cones and the outer nuclear layer together form one layer of neurons. Each rod consists of (*a*) an outer cylindrical segment which is transversely striated, and which, in a dark-adapted retina, contains visual purple or rhodopsin, and (*b*) an inner fusiform segment, vertically striated in its outer fourth and granular in the remaining three-fourths. Each rod is prolonged into the outer nuclear layer as a varicose fibril, in the course of which is a nucleus. The nucleus in some animals is transversely striated. Each fibril ends in a knob in the outer molecular layer, the knobs of several adjacent rod neurons coming into relationship with the dendritic arborisation of

a single rod bipolar of the inner nuclear layer. The cones are shorter and thicker than the rods, and each consists of an outer and an inner segment. The outer segment is conical and is transversely striated. The inner segment is vertically striated in its outer two-thirds and granular in its inner third. The continuation of the cone in the outer nuclear layer is a comparatively thick fibre which contains a nucleus immediately under the outer limiting membrane. The cone fibre

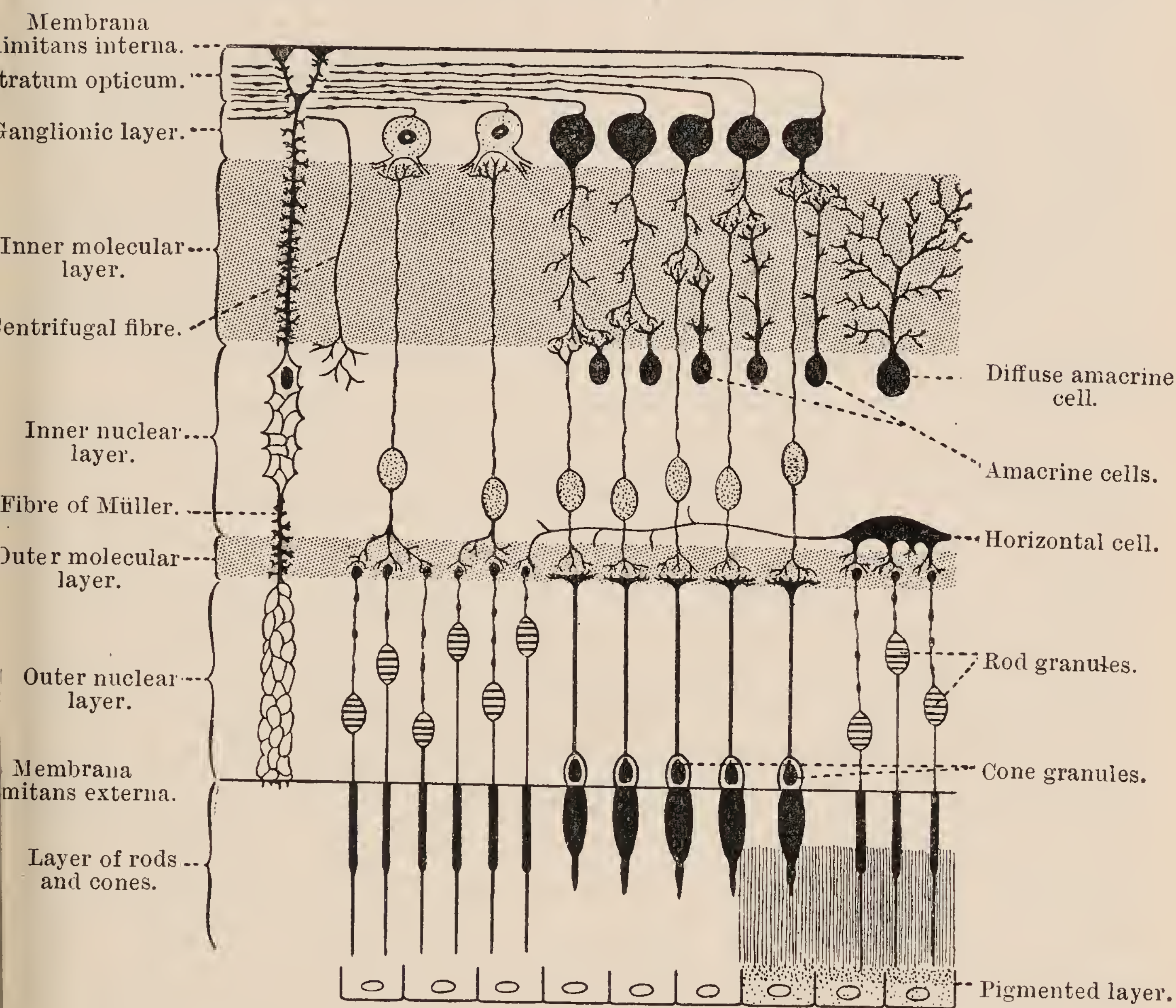


FIG. 33.—Plan of retinal neurons. (After Cajal.) From Gray's *Anatomy.*

terminates in the outer molecular layer by a branched extremity, which is in relationship with the dendritic arborisation of a single cone bipolar of the inner nuclear layer.

(4) and (5) Most of the nuclei of the inner nuclear layer belong to bipolar nerve cells, one fine process from the nucleus passing into the outer molecular layer, the other towards the inner surface of the retina. The outer process ends in a dendritic arborisation in relation either with the knobs of several rod neurons (rod bipolars), or with the terminal branching of a cone neuron (cone bipolars). The inner process of a rod bipolar arborises about the cyton of a cell in the ganglionic

layer; that of a cone bipolar arborises in the inner molecular layer in relation with the dendrons of a ganglionic cell. In the outer part of the inner nuclear layer are horizontal cells, the dendrons and axons of which arborise in the outer molecular layer, so that these cells have an associational function. In the inner part of the layer are cells which have no axons and are therefore called amacrine cells. The dendrons of these cells arborise in the inner molecular layer in relation with the dendrons of the ganglionic cells.

(6), (7), and (8) The cells of the ganglionic layer are arranged in a single row in most parts of the retina. Each has branched dendrons which extend into the inner molecular layer, where they terminate at different levels in relation with the terminal arborisations of the axons of the cone bipolars. The axons of the ganglionic cells are continued as non-medullated nerve fibres in the stratum opticum. Some of the fibres in the stratum opticum have a centrifugal course and run into the retina to terminate by arborisation in the inner nuclear layer.

Three parts of the retina require a special description—the macula lutea, the place of exit of the optic nerve, and the ora serrata.

The *macula lutea* is the part of the retina concerned with distinct vision. When an object is "looked at" its image is formed on the macula, or more particularly on the *fovea centralis*, a small depression in the centre of the macula. At the fovea there are no rods, and the cones are longer than in the remainder of the retina. The cones and their nuclei are the only retinal structures present in the fovea, and the cone fibres are inclined away from the fovea towards the inner nuclear layer. In the peripheral region of the macula the ganglionic layer is several cells deep, and cones are more numerous than rods. The proportion of cones diminishes from the macula to the periphery of the retina, and near the ora serrata very few cones are present. The macula is situated slightly to the lateral side of the posterior pole of the eyeball.

The fibres of the stratum opticum converge to a point about 3 mm. to the nasal side of the macula lutea to form the optic nerve, which passes back through a gap in the choroid coat and a perforated part of the sclera known as the *lamina cribrosa*. The place of exit of the nerve as seen from the interior of the eyeball is a sharply defined pale area, nearly circular in outline, and is called the *optic disc*. At the disc all the retinal layers are absent except the stratum opticum, the fibres of which acquire a myelin sheath as they emerge from the eyeball.

The layers of the retina cease abruptly at the *ora serrata*, and are represented in the ciliary region by two layers of cells, the deeper,

pigmented layer being a continuation forwards of the pigment layer of the retina, and the superficial layer consisting of columnar cells.

THE CONTENTS OF THE EYEBALL.

The cavity of the eyeball is divided into two unequal portions by the crystalline lens and its suspensory ligament. The larger, posterior space is occupied by the vitreous humor (body); the smaller, anterior space by the aqueous humor.

The *crystalline lens* is a biconvex, transparent structure, and lies immediately behind the pupil. It is composed of concentrically arranged fibrous laminæ, made up of prismatic fibres with serrated edges. The central portion of the lens is firmer and denser than the peripheral portion, which is more jelly-like. The posterior surface has a higher degree of convexity than the anterior surface, and rests in the hyaloid fossa of the vitreous body. The lens is enclosed in a structureless capsule, which, towards the equator, is continuous on the anterior surface with the suspensory ligament of the lens. The latter is prolonged backwards as the zonula ciliaris, to be attached to the ciliary processes.

The *vitreous humor* is transparent and resembles a thin jelly, containing a few scattered delicate fibres. It is enclosed in a delicate capsule, the hyaloid membrane, which in the neighbourhood of the ciliary processes is thickened to form the zonula ciliaris. The latter splits in front into two layers, the anterior being the suspensory ligament of the lens, and the posterior lining the concavity in the vitreous body, the hyaloid fossa, in which the lens rests. A canal runs through the vitreous humor from the optic disc to the posterior pole of the lens, and is lined by a continuation of the hyaloid membrane. This canal contains the hyaloid artery in the embryo.

The space in front of the lens is divided into an anterior and a posterior chamber by the iris, and contains the aqueous humor, which is a watery fluid, alkaline in reaction, and containing salts, chiefly sodium chloride, with a trace of protein.

THE NUTRITION OF THE EYEBALL.

The vascular tunic of the eyeball receives the long and short posterior ciliary arteries and the anterior ciliary arteries. The outer layers of the retina receive nourishment by means of lymph derived from the blood-supply to the choroid. The inner layers of the retina have a direct blood-supply through the distribution of the central artery of the retina, which enters the eyeball with the optic nerve. The

cornea is supplied with lymph from the blood-vessels which surround its margin. The veins of the choroid converge to form four or five main trunks, the *venæ vorticosæ*. The blood from the retinal artery is returned by the corresponding retinal vein.

INTRA-OCULAR TENSION.

By inserting a cannula connected with a manometer into the anterior chamber of the eyeball, it can be shown that the contents of the globe exert a pressure on the walls equal to about 25 mm. of mercury. If the intra-ocular pressure be recorded on a revolving drum simultaneously with that of the carotid artery, it will be seen that the two tracings run a parallel course. Obstruction of the descending aorta, for example, causes an immediate rise in both curves, and these remain at the new level till the obstruction is removed, when both fall simultaneously. The chief source of fluid in the eyeball is the vessels of the ciliary processes, and as the pressure of the intra-ocular fluid varies with the blood-pressure, it may be assumed that it is derived from the blood-vessels by a process of filtration. Normally, the addition of new fluid is balanced by the draining away of an equal amount, mainly through the filtration angle and the canal of Schlemm, but also to a very small extent by the posterior lymphatics of the eyeball. In certain diseased conditions this drainage is interfered with, and fluid accumulates in the eyeball, causing a rise of pressure. This condition is known as glaucoma, and if it is not promptly relieved, it results in atrophy of the retina from pressure, and therefore leads to blindness.

The mechanism of transudation of fluid from the ciliary processes and escape of an equal quantity by the canal of Schlemm and posterior lymphatics of the eyeball is not only of importance for the nutrition of the non-vascular contents of the eyeball, but the state of tension which is thereby maintained gives the eyeball the degree of rigidity which is necessary if it is to serve any useful purpose as an optical instrument.

THE FUNCTION OF SIGHT.

The function of sight, in the commonly accepted sense of the word, involves (1) the formation of a real image of external objects in the retina, (2) changes in the retinal end-organs, (3) the transmission of the stimulus due to the retinal changes to the cortex of the occipital lobe, (4) the changes in the cortex, visuo-sensory and visuo-psychic areas, which result in a visual sensation, and (5) the associational processes of comparison of the sensation with previous sensations by which visual judgments are formed.

THE FORMATION OF AN IMAGE IN THE RETINA.

The eyeball may be compared with a photographic camera, the cornea, aqueous humor, lens, and vitreous body forming a system of lenses, the choroid coat being comparable with the dark lining of the camera, and the retina acting as the sensitive plate. If a segment of the sclera with the choroid be excised from the back of the eye of a recently killed ox, and the eye be held in front of an electric lamp, an inverted image of the lamp will be seen upon the retina, similar to the image which may be observed on the ground-glass screen of a camera.

In the camera the image is usually formed by means of a single biconvex glass lens. The optical axis of such a lens is a line drawn through its optical centre, and entering and leaving it in a direction perpendicular to the plane of the lens. A ray of light passing along

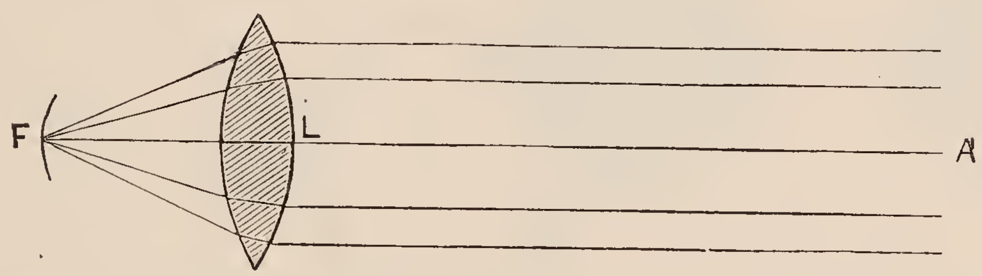


FIG. 34.—Diagram of the course of parallel rays through a biconvex lens (L), by which they are converged to the principal focus (F). A, axial ray. (Starling's *Principles of Physiology.*)

this axis enters and leaves the lens with its direction unchanged, but rays falling upon the lens outside the axial ray and parallel with it are refracted, both on entering and leaving the lens, towards the axial ray, so that they meet it or come to a focus at a point which is known as the principal focus of the lens (fig. 34). A pencil of divergent rays falling upon such a lens will, if the lens have a sufficient degree of convexity, be brought to a focus at a point behind the principal focus. If an object, such as an arrow, be placed at some distance from a biconvex lens, the pencil of rays from the tip of the arrow will be brought to a focus behind the lens, and the same will hold for rays from the butt and every other point on the arrow. The axial ray of each pencil will pass through the optical centre (nodal point) of the lens with its direction unchanged. The result will be the formation of a real, inverted image of the arrow in the plane in which the rays are focussed.

The formation of an image in the eye is more complicated in that the cornea, aqueous humor, lens, and vitreous body form, not a single lens, but a system of lenses differing in refractive index, so that altera-

tion in the direction of rays of light takes place at the anterior surface of the cornea, anterior surface of the lens, and posterior surface of the lens. It has been calculated, however, that the net result of the refraction in the eye is the same as that which would occur in a uniform medium the anterior surface of which is 2·3 mm. behind the anterior surface of the cornea, and the nodal point 0·47 mm. in front of the posterior surface of the lens. Such a theoretical arrangement is known as the reduced or schematic eye (fig. 35).

By means of the schematic eye the size of an image on the retina can be ascertained. In the normal or emmetropic eye at rest parallel rays are brought to a focus on the retina, and for practical purposes rays proceeding from a point 6 metres or more distant from the eye may be regarded as parallel. If, therefore, a diagram of the reduced eye and of an object at 6 metres distance be drawn to scale, and if lines be drawn from the periphery of the object through the nodal point to the retina, the size of the retinal image can be measured. The size of the image of an object nearer than 6 metres can also be calculated, it being assumed that the eye is accommodated for the object. The angle subtended by the object, and therefore by its image in the retina, is spoken of as the visual angle. As the distance of the nodal point from the retina in an emmetropic eye is known (15·5 mm.), the size of the retinal image of an object is easily ascertained if the visual angle is measured.

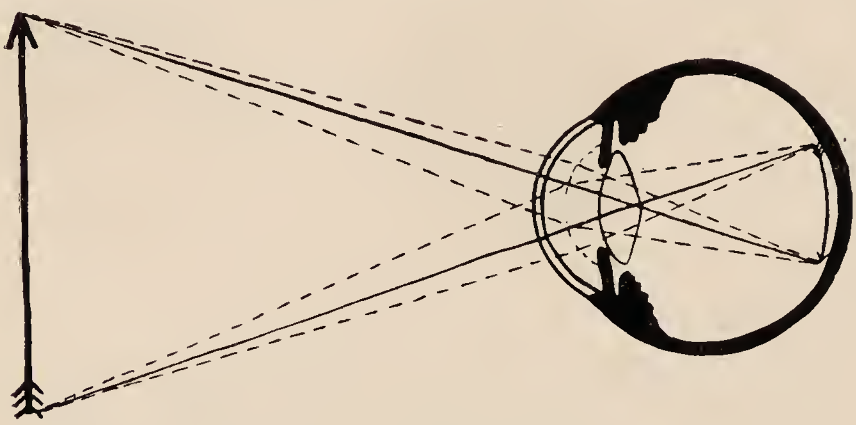


Fig. 35.—Diagram showing formation of an image in reduced eye.

The limit of retinal discrimination corresponds with a visual angle of sixty seconds, that is, in order that two points of light may be distinguished as separate points, they must subtend an angle at the nodal point of not less than sixty seconds. A visual angle of this size corresponds with the diameter of a single cone in the fovea centralis; it subtends a base of 4·38μ on the retina, and the cones in the fovea vary in diameter between 2 and 5μ.

SIGHT-TESTING.

The acuteness of vision is tested either by means of groups of dots of varying sizes or by means of special test types. The test card is usually placed at a distance of 6 metres from the eye to be tested, and

at this range the distance between adjacent dots or the segments of the various letters, as the case may be, subtends visual angles of known size. The visual acuity is expressed as a fraction, of which the numerator is the distance in metres at which the test is made, and the denominator is the distance at which the smallest type read should be distinguished by an emmetropic eye, as, for example, 6/6 (normal), 6/9, 6/12, and so on.

ACCOMMODATION.

An emmetropic eye at rest is in focus for parallel rays, that is, for rays coming from a distance of 6 metres or more. The images of objects within this distance are brought to a focus on the retina by an effort of accommodation. The essential part of the act of accommodation is that the crystalline lens becomes more convex, so that divergent rays are brought to a focus on the retina. On looking obliquely into an eye which is being accommodated for a near object, the alteration in shape of the lens can be observed. The iris can be seen to move forward because of the increasing convexity of the lens. The alteration in shape is limited to the anterior surface, and this can be demonstrated by means of Sanson's images, which are most conveniently observed with the help of an instrument known as the phákoscope. This consists of a triangular box with truncated angles. At one angle is an aperture for the eye of the observer, at another an opening for the observed eye, at the third two triangular openings for the admission of light. Opposite the observed eye is another opening in which a wire is placed. The person who is being observed first relaxes his accommodation by looking through the aperture opposite to him at an imaginary distant object. The source of light is seen to be reflected from his eye at three positions, namely, the anterior surface of the cornea, and the anterior and posterior surfaces of the lens (Sanson's images). The images reflected from the anterior surfaces of the cornea and lens are erect; that from the posterior surface of the lens is small and inverted. If the observed eye be accommodated for the wire opposite it, the middle image only is altered, coming nearer the anterior image and becoming smaller in size (fig. 36). This shows that the anterior surface of the lens moves forward

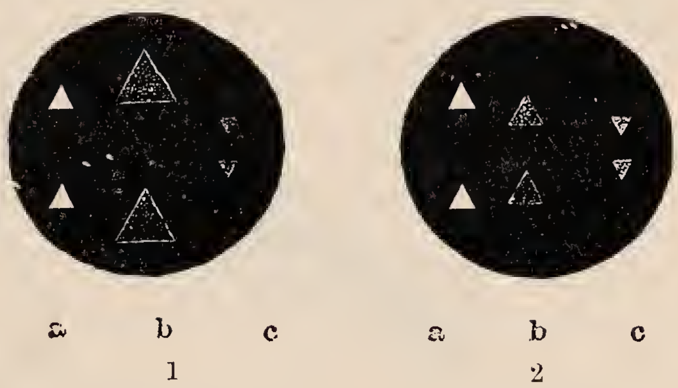


FIG. 36.—Sanson's images, (1) with eye at rest, (2) during accommodation. (Starling's *Principles of Physiology.*)

a, images from anterior surface of cornea; *b*, from anterior surface of lens; *c*, from posterior surface of lens.

in accommodation, and also that it becomes more convex. The absence of movement of the other images indicates that the cornea and posterior surface of the lens remain stationary during accommodation.

The Mechanism of Accommodation.—The lens is an elastic structure, and, as has already been stated, it is enclosed in a capsule which is connected with the ciliary processes by the suspensory ligament. The contents of the eyeball exert a pressure or tension on the coats of the eye, amounting normally to the equivalent of 25 mm. of mercury. In consequence of this tension the suspensory ligament exerts a pull on the lens capsule, and the convexity of the anterior surface of the lens is in this way diminished. When the lens is removed from the eye it assumes a more convex shape in virtue of its elasticity. The same change of shape takes place with the lens in position, when the

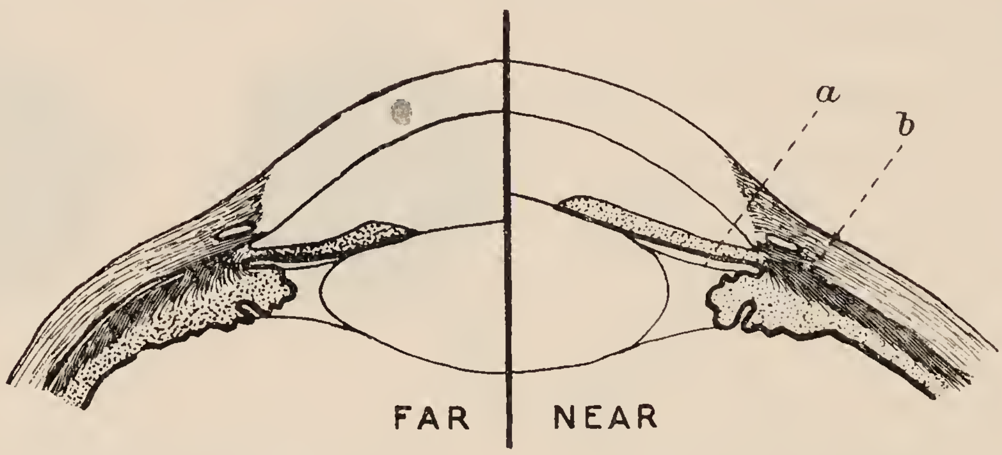


Fig. 37.—Diagram showing mechanism of accommodation. (After Helmholtz and Foster.)

a, suspensory ligament; *b*, ciliary muscle.

tension of the suspensory ligament is diminished during accommodation by the action of the ciliary muscle. Contraction of the radial fibres of this muscle pulls forward the posterior part of the ciliary processes with the attached suspensory ligament, and in this way the latter is relaxed and the lens becomes more convex anteriorly in virtue of its elasticity (fig. 37). The circular fibres of the ciliary muscle also take part in accommodation, approximating the ciliary process to the lens by their contraction. The effect of contraction of the ciliary muscle may be demonstrated by two experiments: (1) by the action of eserine, and (2) by the movement of a needle inserted into the ciliary processes. (1) When eserine is instilled into the human eye, it causes the ciliary muscle and sphincter of the iris to contract, and the slackening of the suspensory ligament can be shown by oscillations of the lens which take place when the head is quickly moved. (2) When the point of a needle is inserted into the ciliary processes in an animal, and the ciliary muscle is stimulated to contract, the end of the needle outside

the eye moves backwards, showing that the point in the ciliary processes has been pulled forward.

When the ciliary muscle contracts in accommodation, there occur at the same time contraction of the pupil and convergence of the eyes. The contraction of the pupil is effected by the sphincter pupillæ, and is of service in sharpening the definition of the image formed on the retina, just as the definition of an image in the photographic camera is improved by the use of a small diaphragm. The convergence of the eyes is effected by the contraction of the internal recti, and results in the image of the object looked at being formed on the fovea of each eye.

In the emmetropic eye the far point (*punctum remotum*) of distinct vision is at infinite distance, while the near point (*punctum proximum*) varies with age. The elasticity of the lens, and consequently the range of accommodation, diminish steadily as age advances, and the near point therefore gradually recedes. This is shown in the following table :—

Age.	Range of Accommodation in Dioptres.	Near Point.
10	14	7 cm.
20	10	10 ,,
30	7	14 ,,
40	4·5	22 ,,
50	2·5	40 ,,
60	1	100 ,,
70	0·25	400 ,,

In civilised life the power of accommodation is called into play more for reading than for any other purpose, and it will be seen from the table that between the ages of forty and fifty the near point recedes to a greater distance than it is convenient to hold a book. Moreover, it is found that the prolonged effort of accommodation required for reading cannot be kept up if more than three-fourths of the total power of accommodation is being utilised. It is therefore necessary, usually about the age of forty-five, to supplement the mechanism of accommodation for reading or other near work by the use of convex lenses of such strength as to bring the near point to a range of about 25 cm. or ten inches. The term *presbyopia* is used to indicate the failure of accommodation which occurs about the age of forty-five.

Accommodation is a voluntary act, and is peculiar in that respect in that the ciliary muscle and the sphincter pupillæ are composed of smooth muscle. Both these muscles, as well as the internal recti, are

supplied by the third cerebral nerve. Definite groups of nerve cells can be localised in the nucleus of the third nerve for each muscle supplied by it, stimulation of particular areas in the nucleus being followed by contraction of particular muscles. The groups of cells for the ciliary muscle, sphincter pupillæ, and internal recti lie close together in the anterior part of the nucleus; and the centre for the internal rectus on each side is connected with that of the sixth nerve of the same side, so that when the internal rectus contracts there is reciprocal relaxation of the external rectus of the same eye.

AMETROPIA.

The condition of the normal or standard eye is called emmetropia, and any departure from the standard is known as ametropia. When the antero-posterior diameter of the eyeball is too short, so that parallel rays are focussed behind the retina, the condition is called hypermetropia; when the antero-posterior diameter is unduly long, so that parallel rays are focussed in front of the retina, the term myopia is used to indicate the defect (fig. 38); when the rays of light entering the eye in one meridian are refracted to a greater or less degree than those which enter in another meridian, the condition is spoken of as astigmatism (fig. 39).

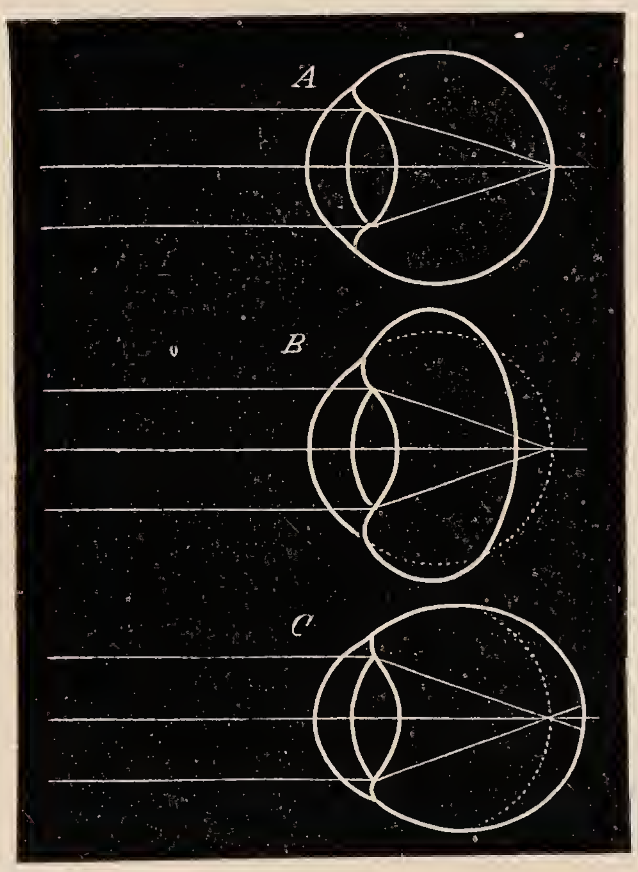


FIG. 38.—Diagrams of course taken by parallel rays on entering the eye. (Starling's *Principles of Physiology.*)

A, an emmetropic; B, a hypermetropic; and C, a myopic eye.

A moderate degree of *hypermetropia* does not necessarily involve defective vision, because the defect is usually compensated by increased power of the ciliary muscle, so that rays of light are focussed on the retina by an increased use of the accommodative mechanism already described. The extra strain involved in this compensatory effort, however, often leads to unpleasant symptoms, and it is advisable in many cases of hypermetropia to correct the error by the use of convex spectacles.

Myopia cannot be overcome by any accommodative act, and distinct vision of distant objects can only be obtained in a myopic eye by the use of concave spectacles, which cause the rays of light entering

the eye to diverge in such a way that they are focussed on the retina.

Astigmatism is usually due to unequal curvature of the cornea, the commonest form showing a greater convexity in the vertical than in the horizontal meridian. In other words, the cornea is not spherical, but resembles the back of a spoon. Consequently the rays entering the eye in the meridian of greater curvature are brought to a focus in front of those which enter in the meridian of lesser curvature (fig. 39), and as a result the eye cannot focus both bars of a cross simultaneously. The defect is counteracted by the wearing of cylindrical lenses, that is, lenses which resemble a vertical section of the superficial part of a cylindrical glass rod.

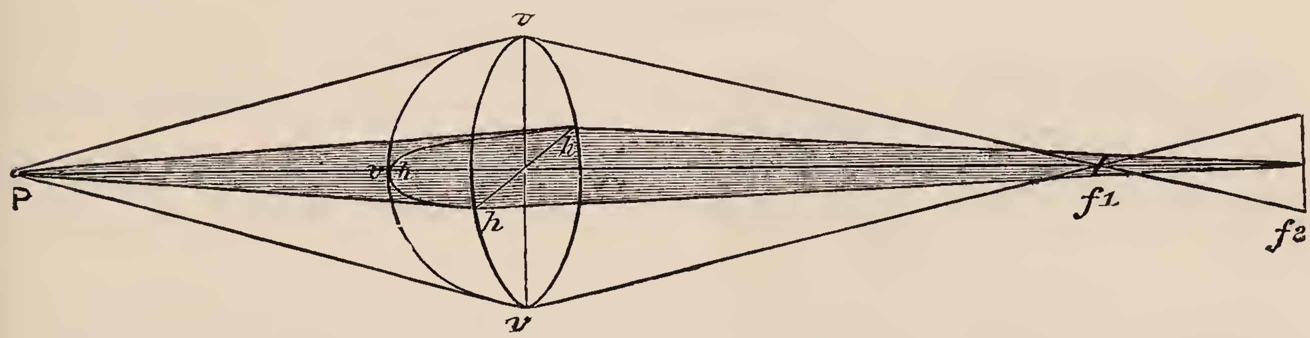


Fig. 39.—Diagram to show the course of rays in an astigmatic eye. (Waller.) From Starling's *Principles of Physiology.*

The rays (from P) in the vertical meridian, *vv*, come to a focus sooner than those in the horizontal meridian, *hh*.

The unit of measurement for degrees of refractive error and for the strength of compensating lenses is the dioptre. This term indicates a lens of such a strength that by it parallel rays are brought to a focus at one metre distance. A 2 dioptre (2D) lens has a focal distance of half a metre, a 3D lens of a third of a metre, a $\frac{1}{2}$D lens of two metres, and so on.

SPHERICAL AND CHROMATIC ABERRATION.

The crystalline lens, like other lenses, has greater refractive power at its periphery than towards its centre, and consequently rays which pass through it near its margin are brought to a focus sooner than those which pass through its centre, and give rise to a certain degree of blurring of the image on the retina. The unequal refraction which produces this result is known as *spherical aberration*, and it is corrected in the eye (1) by the centre of the lens being denser and more highly refractive than the peripheral portion, and (2) by the iris acting as a diaphragm and cutting off the peripheral rays.

By *chromatic aberration* is meant a fault common to all lenses and shared by the crystalline lens, whereby each sector of the lens acts as a

prism, dispersing the coloured rays which are combined in white light. The rays at the violet end of the spectrum are of short wave-length and are more refrangible, and therefore come to a focus sooner than the rays of greater wave-length towards the red end of the spectrum. Consequently the images formed on the retina are surrounded by violet and red halos ; but these do not arouse any sensation, for two reasons : (1) because the rays of medium refrangibility, which are brought to a focus on the retina, are the most luminous, and the effect of the stimulation excited by these is to depress the sensitivity of the adjacent parts of the retina by contrast, and (2) because the visual apparatus is relatively insensitive to the rays at the extreme ends of the spectrum.

THE FUNCTIONS OF THE IRIS.

The pupil varies in size with the degree of light entering the eye and with other conditions, becoming smaller when the sphincter pupillæ contracts and wider on contraction of the dilator pupillæ. We have seen that the pupil contracts with accommodation, and that the result is improved definition of the image on the retina. The improvement is due to the cutting off of the peripheral rays, with the consequent correction of spherical aberration. Secondly, the iris regulates the amount of light entering the eye, and so protects the retina from over-stimulation. If the intensity of the light is gradually increased, the pupil does not contract, but if the increase is sudden, the pupil becomes smaller, and afterwards slowly returns to its former size as the retina becomes adapted to the increased stimulus. On the other hand, in a person in a dark room the pupils are widely dilated and remain in this condition until the eyes are once more exposed to light. The alteration of the pupil with varying degrees of light is due in mammals to a reflex nervous mechanism, the optic nerve conveying the afferent impulses, and the third nerve and sympathetic fibres the efferent impulses, to the sphincter and dilator of the pupil respectively. The fibres to the sphincter travel by the ciliary ganglion and short ciliary nerves, and stimulation of these in any part of their course is followed by constriction of the pupil, while section of the third nerve is followed by dilatation. The dilator fibres emerge from the spinal cord by the first two thoracic anterior roots, and run up in the cervical sympathetic to the superior cervical ganglion, from which post-ganglionic fibres run along the internal carotid artery to the Gasserian ganglion, where they join the ophthalmic division of the fifth nerve and travel to the dilator fibres of the iris by the nasal branch and the long ciliary nerves (fig. 40). Section of the cervical sympathetic nerve is followed by con-

traction of the pupil, and stimulation of the distal end leads to dilatation. As section of the third nerve is followed by dilatation and section of the sympathetic by contraction of the pupil, it is obvious that tonic impulses are constantly passing along both nerves. The fact that dilatation of the pupil is due to active contraction of the radial muscle fibres of the iris, and not merely to relaxation of the sphincter, is proved by two experiments. (1) Localised stimulation of the periphery of the iris leads to contraction of that part of the iris only, and (2) if a sector of the iris be separated by two radial cuts it will contract, either on local stimulation or on stimulation of the sympathetic nerve in the neck. The sympathetic root of the ciliary ganglion contains vaso-constrictor fibres for the vessels of the eye.

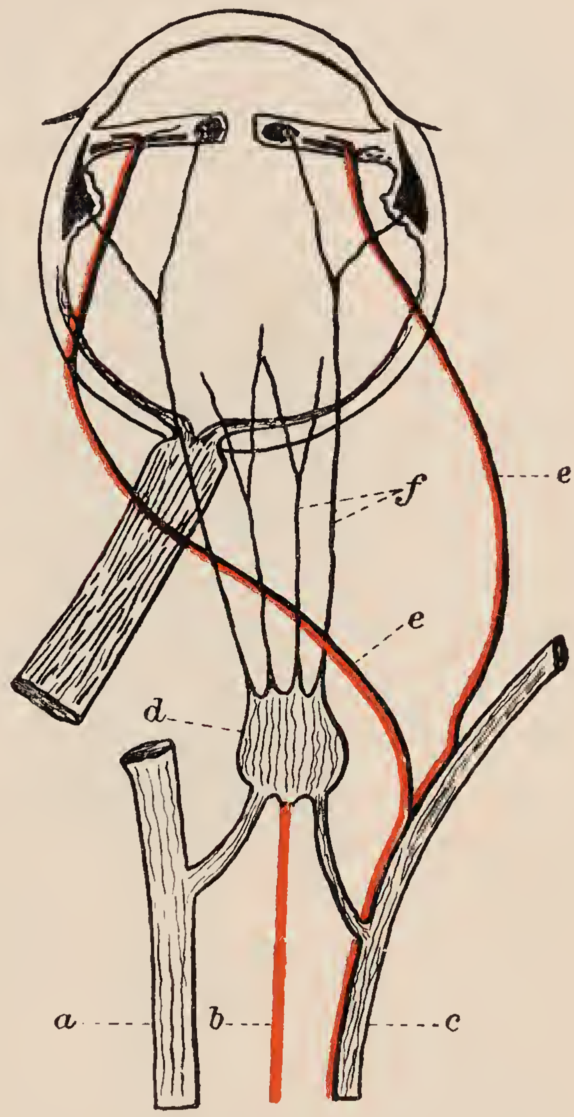


FIG. 40.—Scheme of the nerves the eye (after Foster).

Sympathetic fibres red. *a*, third nerve; *b*, sympathetic root of ciliary ganglion; *c*, nasal branch of fifth nerve; *d*, ciliary ganglion; *e*, *e*, long ciliary nerves; *f*, short ciliary nerves.

In man, and in other animals in which there is a partial decussation of the optic nerves, the reflex contraction of the pupil to light is bilateral, that is, light falling on one eye leads to contraction of both pupils. This is due to the fact that by means of the decussation each optic nerve forms connections with both superior corpora quadrigemina, and thus with the nuclei of both third nerves. If one optic nerve is atrophied, the pupil of that eye will contract when light falls on the other eye, but not when light falls on the affected eye.

Contraction of the pupil occurs not only as a result of the light reflex, but also from other causes. The various factors which bring about diminution in the size of the pupil are:

1. Light falling on the retina, giving the reflex effect already described.

2. (*a*) Accommodation, (*b*) Sleep. In both of these conditions the contraction of the pupil is an associated condition. In accommodation, it occurs simultaneously with the contraction of other muscles supplied by the same nerve; in sleep the eyes are rotated upwards and inwards, and the pupils contract in association with the convergence.

3. Drugs. Morphia taken internally, and eserine or pilocarpine, either taken internally or applied directly to the eye, cause the pupil to contract. Contraction also takes place in the third stage of chloroform or ether anæsthesia.

Dilatation of the pupil occurs :

(1) On the removal of the light stimulus from the eye.

(2) As a result of stimulation of sensory nerves.

(3) In emotional conditions, such as fear.

(4) From the action of drugs, for example, from the internal administration or local application of atropine, or from the local application or intravenous injection of adrenalin. The pupil is also dilated in the early stages of chloroform or ether anæsthesia.

THE RETINAL IMAGE.

When light falls upon the eye it excites chemical, histological, and electrical changes in the retina.

The Chemical Changes.—We have seen that the outer segments of the rods contain a substance called rhodopsin or visual purple. Rhodopsin can be dissolved out of the retina by a solution of bile salts, and it is rapidly decolorised on exposure to light. If an animal be kept in the dark for some time and then killed and its retina examined, the latter will be of a deep red colour, which soon fades on exposure to light. If, on the other hand, the eyes have been exposed to bright light the retina is pale. The effect of light in bleaching rhodopsin is in proportion to its intensity, so that if a rabbit is kept in the dark for a time and then its eye is exposed opposite a window, a picture of the window, called an optogram, is formed on the retina; in the optogram the window pane areas are bleached, while the rhodopsin is not decolorised in the shaded parts corresponding with the bars. As visual purple is not present in the cones, the fovea does not show this chemical change.

The Histological Changes.—In an eye which has been exposed to light fine processes of the pigment cells are found to extend between the rods and cones, the processes themselves being laden with pigment granules, whereas if the animal has been kept in darkness before the examination of its eye, the cells of the pigment layer are flat, the processes being retracted. Further, in some animals, for example the frog, the cones are retracted on exposure to light and extended when the animal is kept in darkness (fig. 41). The cells of the pigment layer have the power of restoring the visual purple, for when a retina, which has been bleached by exposure to light, is laid upon the pigment layer, rhodopsin again appears in the rods.

The Electrical Changes.—When an excised eye is placed in circuit with a string galvanometer, it is found that a current passes through the eye from the posterior to the anterior pole. When light is allowed to fall upon the retina, there is first a small negative variation of this current, followed by a marked positive variation.

THE FUNCTION OF THE RODS AND CONES.

The layer of rods and cones is the part of the retina in which the impulses are excited which give rise to visual sensations. This is proved by three facts. (1) In the fovea, which is the area for most

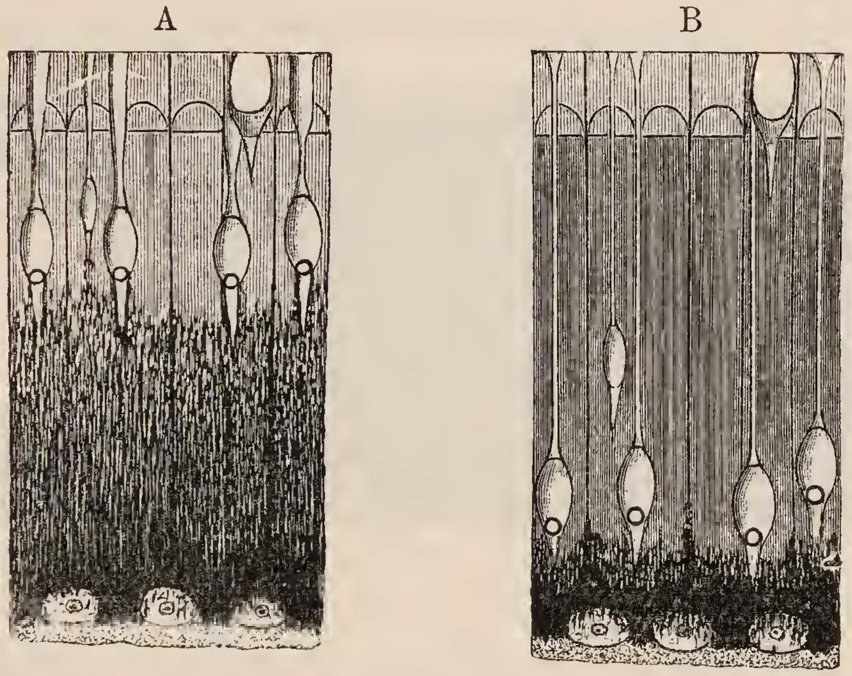


Fig. 41.—Sections of the frog's retina. (From Starling's *Principles of Physiology.*)

A, after exposure to light. B, kept in the dark. (Engelmann.)

distinct vision, cones only are present, the other layers of the retina being absent. (2) No sensation is excited when light falls on the optic disc, where the rods and cones are absent and nerve fibres only are present. The optic disc is therefore called the blind spot, and it is to be noted that there is no sensation of darkness arising from it, but merely the absence of any sensation at all. The existence of the blind spot can be demonstrated in the following way. If the left eye be closed and the right eye gaze steadily at the cross in fig. 42, and if the book be moved to and fro, it will be found that at a distance of about eight inches from the eye the white circle will disappear. The black background will appear to be continuous, showing that the gap is unconsciously filled up. (3) The level of the layer which is stimulated by light can be determined by means of Purkinje's images. If, in a darkened room, a strong beam of light is focussed on the sclera just external to the cornea, images of the retinal vessels will be seen.

If the position of the light is altered, that of the images will also change. The degree of displacement of the light and that of the displacement of the images, as well as the distance of the latter from the eye, being known, the distance between the retinal vessels and the layer of the retina which is stimulated by the shadows can be calculated; and it is found in this way that the structures which are stimulated correspond in position with the layer of rods and cones. The appearance of Purkinje's images is due to the fact that the light, falling from an unusual direction, casts the shadow of the vessels on a part of the retina unaccustomed to such a stimulus.

Inasmuch as the rods and cones are of different structure, it is to be expected that their functions also differ, and there is evidence that

FIG. 42.—(Starling's *Principles of Physiology.*)

this is the case. The cones are most abundant in the central area of the retina, and the rods are in greater proportion in the peripheral part. Associated with this distribution is the fact that central vision is more distinct in ordinary light and peripheral vision more distinct in dim lights. Thus a star which is seen by indirect, or peripheral, vision, may be invisible when the eye is directed towards it. This fact suggests that the cones are adapted for vision in good light and the rods for use in dim light, an assumption which is supported by a comparative study of the retina in animals. In most birds, which go to roost when twilight falls, or even when the sky is obscured by heavy clouds, cones only are present. In owls and bats, on the other hand, which are nocturnal in their habits, there are only rods. The study of the field of vision for colour shows that whereas the central area of the retina is responsive to all coloured rays, the periphery is colour-blind. Moreover, all parts of the retina are colour-blind in dim light.

It is justifiable, therefore, to believe that the cones are functional in good light, and are responsive to stimulation by white and coloured rays, whereas the rods come into play in dim lights and are colour-

blind. It may further be assumed that the function of rhodopsin is to sensitise the rods and so make them more excitable to the weak stimuli for which they are adapted.

Adaptation.—If two persons enter a room in which there is a moderate degree of light, one from bright daylight, the other after being for some time in a dark room, the former will experience a sensation of comparative darkness, whereas the latter may be dazzled. The eyes in the one case are light-adapted, in the other dark-adapted, and the condition of adaptation determines the degree of sensation produced by the stimulus. In the same way, if one goes out of doors from a lighted room at night, at first one must grope one's way, but objects gradually become more distinct as the eyes become adapted to the darkness. After ten minutes the retina is twenty-five times as sensitive as it was on first leaving the bright light. Further, the dark-adapted eye is colour-blind, and must become light-adapted once again before colours can be recognised.

VISUAL SENSATIONS.

Although the sensation of light can be excited by various forms of stimulus applied to the eye, for example by a blow, the adequate stimulus consists of the waves in the ether which emanate from luminous bodies. The sensation of white light results from a compound stimulation, for white light can be dispersed into a series of rays of differing wave-length by passing it through a prism, each particular wave-length giving rise to a different quality of sensation known as colour. The dispersed rays constitute the spectrum of white light, and only some of these act as an adequate stimulus to the retina. The visible rays range from those which give rise to the sensation of red, with a wave-length of 760 millionths of a millimetre, through orange, yellow, green, blue, indigo to violet, with a wave-length of 397 millionths of a millimetre. The ultra-red and ultra-violet rays do not excite any visual sensation.

The images formed upon the retina are merely records of light, shade, and possibly colour. Light and shade are due to varying intensity of white light. The fact that certain objects reflect only particular coloured rays depends upon their property of absorbing the rays which they do not reflect. Thus grass absorbs the rays from both ends of the spectrum and reflects those of the middle, while a scarlet poppy absorbs all the rays of short wave-length, reflecting only the longer waves of the red end of the spectrum.

The invisibility of the ultra-violet rays, or at least of a certain number of them, is due to the fact that they are absorbed by the

refractive media of the eye, especially by the lens. After removal of the lens for cataract, visual sensations may be excited by rays of as short wave-length as 313 millionths of a millimetre. The ultra-violet rays are described as actinic, because they can be detected by their effect on silver salts, for example in a photographic plate.

The ultra-red rays, on the other hand, are not absorbed by the refractive media of the eye, but are invisible because they do not form an adequate stimulus for the end-organs of the retina. They are heat rays, and can be detected by means of a thermometer.

The impulses excited in the retina pass to the occipital lobes of the cerebral hemispheres by the tracts already described (p. 90), those from the left half of each retina reaching the left occipital lobe, and those from the right halves passing to the right lobe. Each tract has cell stations in the thalamus and the external geniculate body. The fovea of the retina is represented bilaterally in the brain.

The impulses conveyed by the optic tracts reach the visuo-sensory area of the cortex, and by means of association fibres are transmitted to the visuo-psychic area. They are then passed on to the great association areas, and, with the aid of the memory of previous visual, tactile, and other sensations, visual judgments are formed, as regards size and distance, shape, depth, and other properties of the objects seen. In connection with the production of visual sensations we have to consider the time required to excite a sensation, the duration of the effect of a stimulus, the result of variations in the degree of stimulation, the effect of adaptation, contrast and fatigue, and, finally, the nature of the sensation.

A certain interval must elapse between the application of a stimulus to the rods and cones and the production of sensation. This *latent period* has not been measured, but it has been ascertained that the reaction time for sight is rather longer than that for hearing or for stimulation of the skin. By reaction time is meant the time taken to make a voluntary movement in response to a given stimulus. This includes time taken in the receptor organ, in the afferent nerve fibres with their intermediate cell stations, in the sensory and psychic areas of the cortex, in the association area and the motor area, and, finally, in the efferent path and in the effector organ. The reaction time for sight is usually about one-fifth of a second, for hearing about one-seventh, and for skin stimulation rather less.

More definite information is available as to the *duration of the effect of a stimulus*. If a bright electric light is looked at for a few seconds and then the eyes are closed, the image of the light will persist for a short time and then fade away. This is known as a positive

after-image, and is best seen on waking from sleep. The same persistence of sensation is the cause of the solid appearance of the spokes in a rapidly revolving wheel. The normal duration of the visual sensation can be measured by means of revolving discs on which are black and white sectors. If the gaze be directed to such a disc while it is revolving slowly, the separate sectors can be distinguished. With an increased speed of revolution the disc appears to be of a uniform shade of grey, at first producing a sensation of "flicker," and later, as the rate of rotation increases, and fusion is complete, showing a uniform and steady grey appearance. If the rate of rotation at which complete fusion occurs and the size of the sectors are known, it can be calculated that the duration of each impression on the retina after the withdrawal of the stimulus is about one-fiftieth of a second. The fusion of sensations is comparable with the fusion of single muscular contractions to produce tetanus.

COLOUR VISION.

The various colour sensations are due to stimulation of the retina by rays of different wave-length, and it has long been a subject of discussion as to whether the various qualities of visual sensation are associated with stimulation of different end-organs or different chemical substances in the retina. Many theories have been put forward, but none of these accounts for all the facts, and only two need be mentioned here.

The *Young-Helmholtz theory* postulates the presence in the retina of three photo-chemical substances, one of which is susceptible to stimulation by the spectral red rays, and to a diminishing extent by the other rays from the orange to the violet; a second, which is affected chiefly by the green rays and to a less extent by those toward either end of the spectrum; and a third, which is mostly affected by the violet rays, and to a diminishing extent by the remainder of the spectrum from indigo to red. Stimulation of all three substances to an equal extent excites the sensation of white. Stimulation mainly confined to the red substance gives the sensation of red, whereas equal stimulation of the red and green substances with slight affection of the violet substance gives rise to the sensation of yellow. The other colour sensations are excited in the same way by varying degrees of stimulation of the three substances.

On this theory there are three primary sensations, and the hypothesis finds its chief support in the facts connected with colour blindness. Total colour blindness is rare, but about 4 per cent. of European males are partially colour blind, the commonest form being

an inability to distinguish between red and green. This defect is associated in some cases with an absence of sensation from the rays of the red end of the spectrum, while in others there is no inability to distinguish the spectral red. Cases of the former type are red-blind, of the latter green-blind, and on the Young-Helmholtz theory they are accounted for by the absence of the red and green elements respectively from the retina.

According to *Hering's theory* there are four instead of three primary colour sensations—red, green, blue, and yellow. These are arranged in pairs, the two colours in each pair being complementary or antagonistic. If a circular disc, coloured one half red and the other half green, is rotated rapidly, the sensations of red and green will be fused and the resulting sensation will be grey, or absence of colour. The same fact holds for blue and yellow. Red and green on the one hand and blue and yellow on the other are therefore antagonistic colours. On Hering's theory there are three photo-chemical substances in the retina, each of which arouses a different sensation according as it is undergoing assimilation or dissimilation. One of these substances is broken down when stimulated by red rays and built up when green rays fall upon it; the second undergoes dissimilation or katabolism under the influence of yellow, and assimilation or anabolism under the influence of blue rays; the third is broken down by white light and built up again in the absence of light.

Hering's theory does not account for the shortening of the red end of the spectrum in those colour-blind persons who cannot distinguish red from green, but it is supported by the effects of fatigue of the visual apparatus and by the facts of simultaneous and successive contrast.

Fatigue of the mechanism connected with visual sensations can be demonstrated by looking fixedly at a bright object for a short time and then transferring the gaze to a white surface, when a dark spot or negative after-image will be seen, corresponding with the position on the retina of the image of the bright object. Owing to the fatigue of the part of the apparatus already stimulated, the white paper does not excite the same sensation in it as in the remainder of the retina. It may be supposed that the white-black substance undergoes active katabolic change as the result of the excessive stimulus, and that this is succeeded by anabolism when the intensity of the stimulus is reduced.

The effect of *simultaneous contrast* may be shown by placing a disc or cross of grey paper on a coloured sheet, and covering the whole with tissue paper. The grey will appear green on a red background, red on

a green, blue on a yellow, and yellow on a blue, the grey strip in each case assuming the colour complementary to that of the background. This phenomenon is supposed by Hering to be due to dissimilation of any one of the three photo-chemical substances in part of the retina, this being accompanied by assimilatory changes in the same substance in the adjacent parts of the retina (or the converse), a process known as "retinal induction."

Successive contrast is seen if one gazes at a coloured disc, for example red, for half a minute or a minute, and then transfers the gaze to a white sheet. The complementary colour will be seen on the sheet: it is green if the original disc be red, blue if it be yellow, and so on, and it constitutes one form of negative after-image. On Hering's theory the after-image is due to anabolic changes following katabolic, or *vice versa*. On another theory, however, the phenomenon is ascribed to changes in the cortex of the cerebral hemisphere.

THE MOVEMENTS OF THE EYEBALL.

In a state of rest the two eyeballs lie in the orbital cavities with their optic axes projecting horizontally forwards and parallel with each other. Conjugate movements of the two eyes take place, either upwards or downwards, or to the right or left; or certain of these movements may be combined or may be accompanied by rotation of the eyeballs. Further, during accommodation there is a movement of convergence of the eyeballs.

These various movements take place about the three principal axes of each eyeball, the antero-posterior, vertical, and horizontal axes, and are effected by the six extra-ocular muscles of each eye. The cornea is rotated upwards and inwards by the superior rectus, upwards and outwards by the inferior oblique, and directly upwards by the combined action of these two muscles. The inferior rectus rotates the cornea downwards and inwards, the superior oblique turns it downwards and outwards, and both these muscles together turn it directly downwards; the internal rectus rotates the eyeball inwards, the external rectus turns it outwards. The cornea may be rotated into intermediate positions by the combined action of two or more muscles acting together. When any one muscle contracts there is reciprocal relaxation of its antagonist; thus contraction of the internal rectus is accompanied by relaxation of the external rectus of the same eye.

The external rectus is supplied by the sixth, the superior oblique by the fourth, and the remaining muscles, together with the levator palpebræ superioris, by the third cerebral nerve.

In man vision is binocular, and the eyeballs always move together in such a way that the image of the object looked at falls on the fovea of each eye. If the object is a distant one, the visual axes are parallel; if the object is a near one, there is convergence of the visual axes. In either case objects which are not in the direct line of vision fall on "corresponding points" of the two retinæ. If the mechanism for combined movements fails for any reason, the images of external objects are not formed on corresponding points, and double vision, or diplopia, results.

THE FIELD OF VISION.

When an object is looked at its image is formed on the fovea, and it is seen distinctly. This is known as "direct vision." At the same time, surrounding objects are focussed on the retina outside the fovea and are seen less distinctly. This is known as "indirect vision." The extent of the outer world included in both direct and indirect vision constitutes the visual field, and is measured by means of an instrument called the perimeter. A simple form of this consists of a graduated arc which can be moved into any meridian, and which is provided with a white spot at its axis. The subject closes one eye, and with the other gazes steadily at the white spot. A white or coloured object is then moved from the extreme end of the arc until it comes into the field of vision, when its position is recorded on a chart. This is repeated for other meridians, and then the recorded points are connected on the chart by lines, thus giving a map of the field of vision. The field for a white object is larger than that for a coloured object, and, of the primary colours, blue and yellow have the largest field and green the smallest, while red is intermediate (fig. 43).

Fig. 43.—Perimetric chart for right eye, showing fields for white, blue (and yellow), red, and green. (After Howell.)

The field for white extends to 90° on the temporal side, about 80°

downwards, 65° to the nasal side, and 50° upwards. The field on the nasal side is obstructed by the bridge of the nose, but the area of the retina on which the obstructed rays would fall is insensitive. When both eyes are in use, the fields of vision overlap, so that the combined field extends to 65° on either side of the central point, that is, the point which is focussed on the fovea.

VISUAL JUDGMENTS.

The flat picture formed on the retina gives rise to sensations of light, colour, and shade. These sensations are conveyed to the association areas of the brain, where the interpretation of the picture, or visual judgment, takes place. If, for the sake of simplicity, the image of a single object be considered, judgments are formed as to its position in space, its distance from the eye, its size, form, and solidity. These judgments are based partly on the visual sensation, partly on previous experience derived not only from vision but also from the other senses. A new-born infant is unable to interpret its visual sensations, but it gradually learns to correlate these with tactile and other impressions, until finally the visual sensation alone conveys impressions which at first were dependent on other senses as well as that of sight.

An object can be localised as the result of experience that an image on a given part of the retina corresponds with a definite position in space. The image on the retina is inverted, but the object is seen in the upright position because the interpretation of the image is again the result of experience. The retina, in fact, acquires "local sign."

Experience also enters largely into judgments of size and distance, and the latter are closely related to each other. If the size of an object is known, its distance is estimated by the visual angle which it subtends; in other words, by the size of its image on the retina. On the other hand, if the distance of an unfamiliar object is known, its size can be judged in the same way. Other factors, however, enter into judgments of distance. If the object is close at hand, the degree of convergence of the eyes and of accommodation required to see it distinctly are of assistance. The importance of convergence can be shown by holding a pencil vertically about 40 cm. from the face and attempting to touch it from one side with another pencil, first with one eye closed, and then with both eyes open. If the object is distant, its outline is more or less indistinct, owing to the fact that the atmosphere is never perfectly transparent, and the degree of blurring varies with the distance. The estimation of the size and distance of an unfamiliar object at an unknown distance is assisted by comparison with other objects which

are more familiar, and the relation in space of which to the unfamiliar object can be determined.

The judgment of solidity is dependent mainly on binocular vision. A solid object not too far away from the eyes gives rise to a slightly different image in each eye, and the fusion of these images in consciousness results in the idea of solidity. The same fact is made use of in connection with the stereoscope. Two pictures taken from slightly different points of view are fused by means of prisms, and in this way give the impression of depth which cannot be obtained from a single flat picture.

Binocular vision is thus of the greatest importance in assisting the formation of judgments of the solidity of objects, and still more in estimating accurately the position of those which are close at hand. It follows, therefore, that whereas the permanent loss of an eye involves a certain diminution of the field of vision, it also involves the much greater disadvantage of increasing the difficulty of making the visual judgments on which depend the performance of accurate mechanical work.

Fig. 44.—Zöllner's lines. (Starling's *Principles of Physiology.*)

OPTICAL ILLUSIONS.

It follows from what has been said as to the interpretation of visual sensations that the judgments based upon these are exceedingly fallible, and that this is so is a matter of everyday knowledge. Judgments based upon experience are biassed by that experience, as is well shown by the accompanying illustration (fig. 44), in which parallel lines appear to be alternately convergent and divergent because of the short oblique cross lines. Another simple illustration may be made by taking two straight lines of equal length and drawing divergent lines away from the ends of the one and centralwards from the ends of the other, when the former will appear the longer of the two.

SECTION IV.

THE SENSE OF HEARING.

The ear consists of three parts, the outer, middle, and inner ear. The outer ear consists of the pinna and the external auditory meatus. The pinna is functionless in man, but in some of the lower animals it serves to collect the sound waves and conduct them to the meatus, along which they are transmitted to the membrana tympani. The meatus is about 2·5 cm. in length, and is directed inwards and forwards. It is slightly curved in its course, the convexity of the curve being upwards; in consequence of the curve it is difficult for foreign bodies to reach the membrana tympani, which stretches across the inner end of the meatus.

THE MIDDLE EAR.

The middle ear or tympanic cavity consists of a chamber in the temporal bone containing a chain of ossicles by which the sound waves are transmitted to the internal ear (fig. 45). The cavity is bounded laterally by the membrana tympani, its medial, superior, inferior, and posterior walls are bony, and anteriorly it exhibits two openings, that of the Eustachian tube (auditory tube) below, and the canal for the tensor tympani muscle above.

The membrana tympani, which separates the external from the middle ear, lies obliquely, and is shaped like a shallow funnel with the concavity outwards, the central depression being called the umbo. The membrane is semi-transparent and is composed of three layers, an outer cutaneous layer continuous with the skin lining the meatus, an inner mucous layer formed of the mucous membrane lining the tympanic cavity, and a middle fibrous layer composed of radial and circular fibres.

Two openings are present in the medial wall of the tympanic cavity, both bridged across by membrane in the fresh condition. One, the fenestra ovalis (fenestra vestibuli), is oval in shape; the other, the fenestra rotunda (fenestra cochleæ), lies below and behind the fenestra ovalis.

The ossicles of the middle ear are three in number, the malleus, incus, and stapes. The malleus, or hammer bone, consists of a head and two processes, the longer of which (the handle) is attached to the tympanic membrane, its tip reaching to the umbo, while the shorter process, the processus gracilis, projects anteriorly. The posterior surface of the head of the malleus articulates with the body of the incus by a saddle-

shaped joint of such a nature that, when the head of the malleus moves outwards, a cog-like process upon it is locked in a corresponding depression on the incus. If, however, the head of the malleus moves inwards, the joint surfaces separate, and in this way traction on the membrane enclosing the internal ear is avoided. The incus, or anvil bone, consists of a body and two processes (crura). The body articulates with the malleus, and the longer of the two processes with the stapes. The stapes, or stirrup bone, articulates by its head with the long crus of the incus, and its base is attached to the membrane which closes the

FIG. 45.—Scheme of ear. (After Landois.)

fenestra ovalis. The head of the malleus is attached by an anterior, a superior, and a lateral ligament to the wall of the tympanic cavity, and the short process of the incus is attached by a ligament to the posterior wall of the cavity. As the result of these attachments the malleus and incus can be rotated only around an axis which passes through the processus gracilis of the malleus and the short process of the incus. This movement of rotation takes place when the handle of the malleus moves inwards with the membrana tympani, the head of the malleus and body of the incus moving outwards, and the long process of the incus moving inwards and exerting pressure through the stapes on the membrane in the fenestra ovalis. The movements of the

ossicles are controlled to some extent by the tensor tympani, which is inserted near the root of the handle of the malleus, and the stapedius, which is inserted into the neck of the stapes.

The Eustachian tube connects the cavity of the tympanum with that of the pharynx. It is generally closed, but is opened each time swallowing occurs. When it opens, the air pressure in the middle ear is adjusted to that of the atmosphere, and in this way the tympanic structures are protected from the injurious effects of too small or too great a pressure on the membrana tympani.

THE INTERNAL EAR.

The internal ear consists of a series of cavities in the temporal bone, forming the osseous labyrinth, within which is a corresponding series of membranous structures, the membranous labyrinth. The osseous labyrinth contains a clear fluid, the perilymph; the membranous labyrinth is filled with a similar fluid, the endolymph.

The anterior portion of the labyrinth, or cochlea, contains the end-organs of hearing; the posterior part is concerned with the sense of position, and will be described later.

The Cochlea.—The cochlea consists of a tube coiled in a spiral fashion round a central bony modiolus and making altogether two and a half turns round the latter. A bony ridge projects from the modiolus into the tube and is known as the osseous spiral lamina; attached to this is a membrane, the basilar membrane, which extends to the outer wall of the tube, where it meets a fibrous projection, the spiral ligament. A relatively thick layer of connective tissue, the *limbus laminæ spiralis*, rests on the osseous spiral lamina, and ends abruptly near the basilar membrane by an overhanging border. A delicate membrane, the vestibular membrane or membrane of Reissner, is attached to the upper surface of the limbus and to the wall of the tube in such a way as to cut off a portion, triangular in area, known as the canal of the cochlea (ductus cochlearis). The bony tube is thus divided by the membrane of Reissner and the osseous spiral lamina with the basilar membrane into three divisions, the scala vestibuli above Reissner's membrane, the canal of the cochlea already described, and the scala tympani. The scala vestibuli and scala tympani form part of the bony labyrinth and communicate at the apex of the cochlea by the helicotrema. The scala tympani is closed at its lower end by the membrane in the fenestra rotunda. The scala vestibuli and scala tympani contain perilymph. The canal of the cochlea forms part of the membranous labyrinth and contains endolymph. It communicates

with the saccule of the posterior part of the membranous labyrinth by a fine tube, the *canalis reuniens.*

The Organ of Corti.—The end-organ for hearing lies in the canal of the cochlea and is called the organ of Corti. It consists of a specialised epithelium resting on the basilar membrane (fig. 46). On section the epithelium is seen to be arranged in relation with two rows of rod-like cells, the rods of Corti, which are inclined towards each other in such a way as to form a tunnel. The basal ends of the rods are expanded, and in the angle which each forms with the basilar membrane is a small nucleated mass of protoplasm. The free end of each outer rod is shaped like the head of a swan, the back of it fitting into the end of the inner rod, which resembles the proximal end of the ulna.

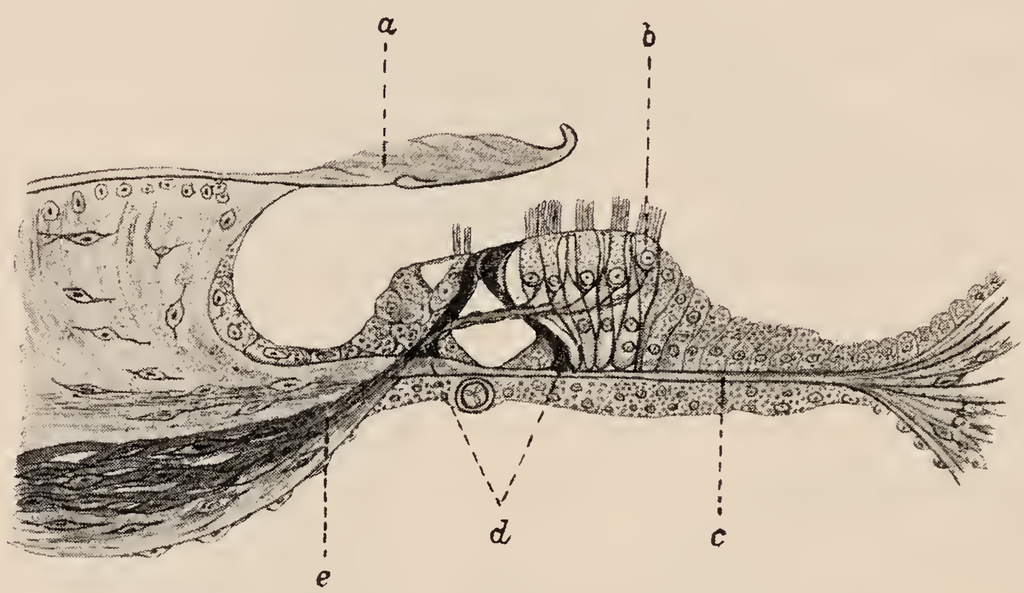


Fig. 46.—Structure of organ of Corti (diagrammatic).

a, membrana tectoria; *b*, hair cell; *c*, basilar membrane; *d*, rods of Corti; *e*, cochlear nerve fibres and (on the left) spiral ganglion.

It is estimated that there are about 6000 inner, and about 4000 outer, rods. The heads of the outer rods are continued outwards as phalangeal processes which unite with corresponding processes on the outer supporting cells to form the reticular membrane.

On either side of the rods of Corti are hair cells, a single row on the inner side, four or five rows on the outer side; the free ends of the outer cells occupy the apertures in the reticular membrane. The hair cells are supported by the cells of Deiters. Beyond the hair cells the supporting cells become shorter, and the epithelium is continuous with the flattened cells lining the canal of the cochlea.

A thick membrane, the *membrana tectoria*, extends from the limbus laminæ spiralis so as to rest upon the organ of Corti.

The fibres of the cochlear nerve occupy the centre of the modiolus and are distributed along the spiral lamina. They are the central processes of the bipolar cells of the spiral ganglion, which lies in the

spiral lamina. The peripheral processes of these cells emerge from the spiral lamina to be distributed as fibrils over the hair cells of the organ of Corti.

THE MECHANISM OF HEARING.

When sound waves fall upon the tympanic membrane they cause the latter to vibrate. The membrane has no periodicity of its own, partly because of its peculiarities of structure, and partly because its vibrations are damped by the attached handle of the malleus. With each inward movement of the membrane the handle of the malleus and the long process of the incus also move inwards, the latter carrying the stapes with it. The malleus and incus together form a lever, the fulcrum of which is the axis of movement described above, the handle of the malleus being the power arm and the long process of the incus the load arm. The length of the handle of the malleus is to that of the process of the incus as 3 to 2, and it therefore follows that the movement of the tympanic membrane is diminished in amplitude in the proportion of 3 to 2, while at the same time it is increased in force by one half, or in the proportion of 2 to 3. Further, as the membrana tympani is twenty times the size of the membrane in the fenestra ovalis on which the vibrations are directed, it follows that the pressure of a sound wave on the membrana tympani is increased to thirty times in its passage across the middle ear ($3/2 \times 20 = 30$).

The vibrations of the membrana tympani, transmitted by the chain of ossicles to the fenestra ovalis, set up corresponding vibrations in the perilymph; these travel up the scala vestibuli and down the scala tympani. The wave in the perilymph is communicated through the delicate membrane of Reissner to the endolymph of the canal of the cochlea, and thus the stimulus is conveyed to the organ of Corti. The increase of pressure in the canal of the cochlea is passed on to the scala tympani, causing the membrane which closes the fenestra rotunda to bulge towards the middle ear.

The adequate stimulus for the organ of Corti is the wave set up in the endolymph as the result of sound waves in the air. Sound waves consist in an alternate condensation and rarefaction of the gases of the atmosphere, and they travel through the air at a rate of about 350 metres a second. They give rise to two kinds of sensation, one that of noise, when the sound waves follow each other irregularly, the other that of a musical note, when the waves follow one another with a certain rhythm.

Musical sounds vary in pitch, in intensity, and in timbre or quality. (1) *Pitch* depends on the rapidity of the vibrations constituting the

10

note, and the more rapid the vibrations, the higher the pitch. The highest note which can be appreciated by the human auditory apparatus has a frequency of about 40,000 vibrations per second, but some animals can detect sounds of higher pitch than this. The lowest note used in music, that of the sixty-four foot organ pipe, has a frequency of sixteen vibrations per second, and gives an impression rather of vibration than of sound.

(2) *Intensity* or *loudness* depends on the amplitude of the vibrations giving rise to the note. This can be shown by recording the vibrations of a tuning fork on a moving drum, when it is seen that the more extensive the movement of the fork, the louder is the note produced by it.

(3) *Quality* or *timbre* is due to the form of the wave. In the case of the tuning fork the wave is simple, and the note is a pure one uncombined with any secondary vibrations. The notes produced by musical instruments, on the other hand, owe their distinctive quality to the production of overtones, which combine with the fundamental note and produce a compound wave. A violin string, for example, not only vibrates as a whole, giving the fundamental note, but also vibrates in segments, producing the overtones which are due to the vibration of halves, thirds, fourths, and still smaller segments of the whole string. The particular quality of the tones produced by any instrument depends upon the number and degree of prominence of the particular overtones.

When two notes are sounded together, the result may be, on the one hand, consonance or harmony, or, on the other hand, dissonance or discord. Discord is due to the fact that the two notes have nearly the same vibratory period, with the result that at certain intervals the summit of one wave occurs at the same instant as the trough of the other, so that the two neutralise each other, causing a momentary silence. Later, the summits of the two waves will correspond, and the degree of sound will be momentarily increased. The rapidly alternating increase and diminution in volume of the sound wave constitutes what is called a beat, and gives rise to the jarring sensation known as discord. When two notes sounded together give a sensation of harmony, there are no such beats, the two waves being combined to form a compound wave of regular rhythm.

The auditory mechanism is not only capable of appreciating sounds, but also of distinguishing differences of pitch within limits, and even, in the case of trained musicians, of analysing a combination of notes, sounded together, into its constituents. Various theories have been held as to the part played by the different structures in the cochlea and by the cerebral cortex itself in the discrimination of pitch, but it will only

be necessary here to state the known facts and the view, based upon these, which is most generally held.

(1) It is a well-known physical fact that a string which vibrates with the rhythm of, say, middle C, will be thrown into vibration if that note is sounded near it. Similarly, if a vibrating tuning fork be held over the mouth of a tall glass jar and water be slowly poured into the jar, when the water is at a certain depth the sound of the tuning fork will be intensified by the resonance of the column of air in the jar.

(2) From the distribution of the cochlear nerve fibres around the hair cells, it may be assumed that the latter are the end-organs for hearing.

(3) The rods of Corti are not present in the cochlea of birds, and are therefore not an essential part of the auditory mechanism.

(4) The basilar membrane is composed of about 24,000 radial fibres, and it increases in width from the base to the apex of the cochlea, the shortest fibres being 0·041 mm. and the longest 0·495 mm. in length.

(5) Experimental destruction of the base of the cochlea in dogs made the animals deaf to high notes, whereas destruction of the apex resulted in deafness to low notes. Similar results have followed disease in man.

These facts suggest that different parts of the basilar membrane resonate to notes of different pitch, the longer fibres responding to low notes and the shorter fibres to high notes. The vibrations of the basilar membrane set up waves in the endolymph, by which the hair cells are stimulated, after-vibrations being damped by the tectorial membrane. On this theory, the analysis of sound takes place in the cochlea, each note causing definite fibres of the basilar membrane to resonate, and thus acting as a stimulus to the hair cells opposite that part of the membrane. If this hypothesis is correct, a note of any particular pitch will always excite an impulse in the same nerve fibres.

The auditory impulses reach the cerebral cortex of the temporal lobe by the auditory tract (p. 91), arriving first at the audito-sensory area, and being transferred to the audito-psychic area. The further conveyance of the impulses to the association areas enables judgments to be arrived at as to the nature of the sounds, as, for example, the rumbling of thunder or the meaning of spoken language.

In some of the lower animals the judgment of the direction from which a sound proceeds is aided by movement of the external ears. In man the projection of sound is more difficult, especially if its source is in line with the mesial plane of the body. Some assistance is obtained by moving the head and noting to which ear the sound is more distinct in each position. As a rule, man relies largely on the co-operation of sight

to localise the direction of a sound, and a blindfolded person has great difficulty in forming a judgment as to the source of a brief sound produced in line with the mesial plane of his body.

VOICE AND SPEECH.

Voice is a musical note produced by the vibration of the vocal cords of the larynx and modified in character by the resonating chambers formed by the upper respiratory passages, the mouth, the accessory sinuses of the nose, and the chest. The vocal cords are thrown into vibration by expiratory currents of air from the lungs.

The framework of the larynx is formed of cartilages connected by fibrous tissue. The *cricoid* cartilage, resembling a signet ring in shape, is connected with the upper cartilage of the trachea by a fibrous membrane; the broad part of the cartilage is situated posteriorly. The *thyroid* cartilage is formed of two laminæ which join in the middle line anteriorly and are separate behind. The lower part of the posterior border of each lamina articulates with the outer aspect of the cricoid cartilage, so that the latter rotates to a limited extent on the thyroid. The *arytenoid* cartilages, right and left, are pyramidal in shape, the base of each articulating with a facet on the upper border of the posterior portion of the cricoid. The *corniculate* cartilages are small, and articulate with the apices of the arytenoid cartilages. The *cuneiform* cartilages are elongated in shape and lie in the aryepiglottic folds. The *epiglottis* is leaf-shaped, the stalk being attached to the recess of the thyroid cartilage, and the flattened portion extending nearly vertically upwards.

The thyroid and cricoid cartilages and the greater part of each arytenoid consist of hyaline cartilage. The apical parts of the arytenoids, the corniculate cartilages, the cuneiform cartilages, and the epiglottis consist of yellow elastic fibro-cartilage.

The lining membrane of the larynx is thrown into two antero-posterior horizontal folds from the recess of the thyroid cartilage in front to the anterior or vocal process of the base of each arytenoid cartilage behind. These are known as the vocal cords (vocal folds), and the slit which they bound is called the glottis (fig. 47). At a slightly higher level there are two parallel folds, the false vocal cords (ventricular folds). The recess between the true and false vocal cords is called the ventricle.

The mucous membrane of the larynx is lined by columnar ciliated epithelium, but the anterior surface and upper half of the posterior surface of the epiglottis, the vocal cords, and scattered patches of the

membrane above the level of the glottis are covered by stratified squamous epithelium.

The glottis is opened by the posterior crico-arytenoid muscles, which by their contraction rotate the arytenoid cartilages on their vertical axis in such a way that the vocal processes are turned outwards. Rotation of these cartilages in the reverse direction is effected by the lateral crico-arytenoid muscles, contraction of which approximates the vocal cords. The closure of the glottis is assisted by the contraction of the arytenoid muscles, which, by approximating the arytenoid cartilages, bring together the posterior ends of the vocal cords. The crico-thyroid muscles by their contraction cause the cricoid to rotate on the thyroid cartilage, so that the broad part of the former is drawn downwards and backwards and the vocal cords are made tense. The general action of the thyro-arytenoid muscles is to draw the arytenoid cartilages towards the anterior part of the thyroid and so relax the vocal cords.

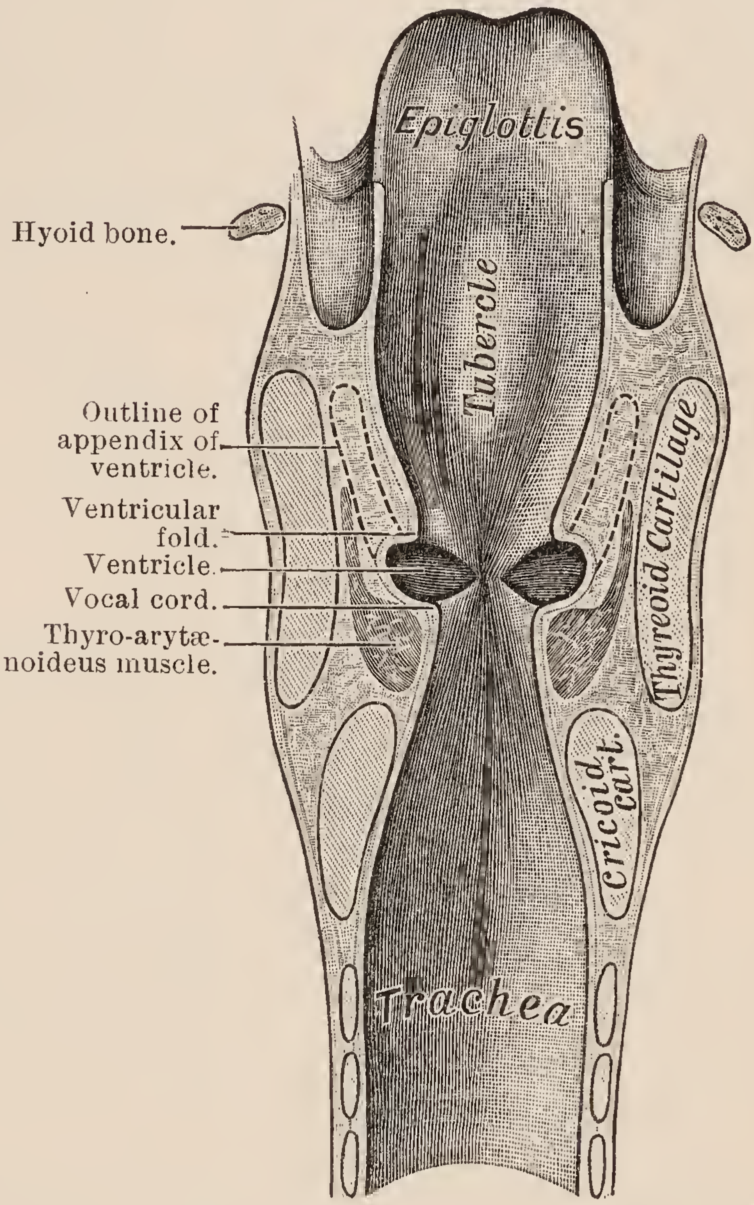


FIG. 47.—Coronal section of larynx and upper part of trachea. (Gray's *Anatomy.*)

The movements which occur in the larynx in connection with swallowing and breathing will be referred to in the descriptions of deglutition and respiration. The changes which occur in the larynx during voice production are observed with the aid of the laryngoscope. This instrument consists of a mirror which can be held in position in the pharynx so as to give a reflected image of the interior of the larynx to the eye of the observer. In such an image the vocal cords appear white, the false vocal cords more pink in colour.

When a note is produced the vocal cords are brought close together, and an expiratory current of air causes them to vibrate. The current

of air must have a certain pressure, and this is produced by contraction of the muscles of the thorax and abdomen which are concerned in expiration.

The note produced may vary in loudness, pitch, and quality or timbre. The degree of loudness varies with the force of the expiratory current. The pitch is determined partly by the length and partly by the tension of the vocal cords. In children the pitch is relatively high, because the cords are short. At the time of puberty the larynx increases considerably in size, more so in the male than in the female, and as a result a boy's voice "breaks," that is, becomes much lower in pitch. The possible variation in pitch in any individual is on an average about two octaves. This is mainly due to variations in the tension of the vocal cords brought about by the reciprocal action of the crico-thyroid and thyro-arytenoid muscles. The pitch is also affected by the length of the vocal cords free to vibrate, this being determined by the movements of the arytenoid cartilages. Further, the force of the expiratory current influences the pitch, the stronger the blast of air the higher being the note produced.

The quality of the note is due to the resonance produced in the various resonating chambers, the air in the chest vibrating with the lower notes and that in the mouth and pharynx and in the accessory sinuses of the nose with the higher pitched notes. Hence the terms chest notes and head notes used in connection with singing.

The sounds which constitute speech are due to modifications of the laryngeal simple note, and are brought about by alterations in the shape of the mouth and in the adjustment of the lips and teeth. The vowel sounds are continuous vibrations, whereas the formation of consonants depends on the interruption of vibrations.

For the production of the broad "a" vowel sound, the mouth cavity is widely open; for the "i" (ee) sound, the space between tongue and palate is much reduced; for "u" (oo), the posterior part of the tongue is raised against the palate.

Consonants are classified as dental, guttural, or labial, according to the position at which the interruption of the laryngeal note takes place. Thus "t" and "d" are dentals, "p" and "b" are labials, and "g" and "k" are gutturals.

In whispering there is no phonation; the glottis is open, and the words produced are the result of the modification of the air current by the speech mechanism.

SECTION V.

PROPRIOCEPTIVE SENSES.

Our knowledge of the position of the body is derived partly from tactile and visual impulses, and partly from impulses reaching the central nervous system from the posterior part of the labyrinth and from the skeletal muscles; the impulses arising in the muscles and labyrinth are called proprioceptive impulses.

The Labyrinth.—The part of the bony labyrinth behind the cochlea consists of a cavity called the vestibule, into which the scala vestibuli opens in front and three semicircular canals open behind. Within the

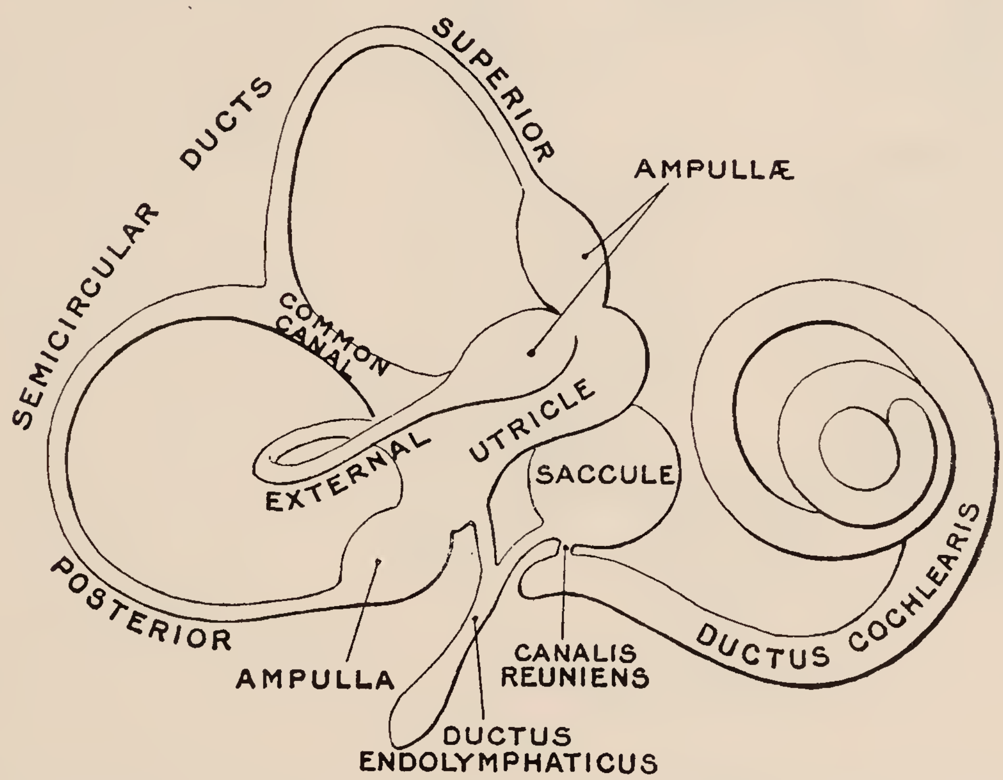


Fig. 48.—The membranous labyrinth. (Enlarged.) Gray's *Anatomy*.

bony semicircular canals lie the three membranous semicircular canals (ducts). The latter open into the membranous utricle, which, along with the saccule, occupies the vestibule, the utricle and saccule being connected by the saccus (ductus) endolymphaticus (fig. 48). The semicircular canals are arranged in three planes at right angles to one another. The external canal lies in the horizontal plane; the superior vertical canal and the posterior vertical canal lie in vertical planes at right angles to one another, as shown in fig. 49.

The canals open into the utricle by five orifices, one of which is common to the medial end of the superior and the upper end of the posterior canal; each canal has a dilatation or ampulla at one end.

The utricle, saccule, and semicircular canals are lined by flattened epithelium resting on connective tissue; in each ampulla the connective

tissue is thickened at one point to form a projection, which is covered with columnar epithelium supporting a number of cells provided with hairs, and which is called the *crista acustica* (*septum transversum*). Similar thickenings occur in the utricle and saccule, these being called *maculæ acusticæ*; they have the same structure as the cristæ, with the addition of small concretions of lime, called otoliths, scattered among the processes of the hair cells. The fibres of the vestibular nerve are distributed to the cristæ and maculæ acusticæ, and end in fibrils round the hair cells.

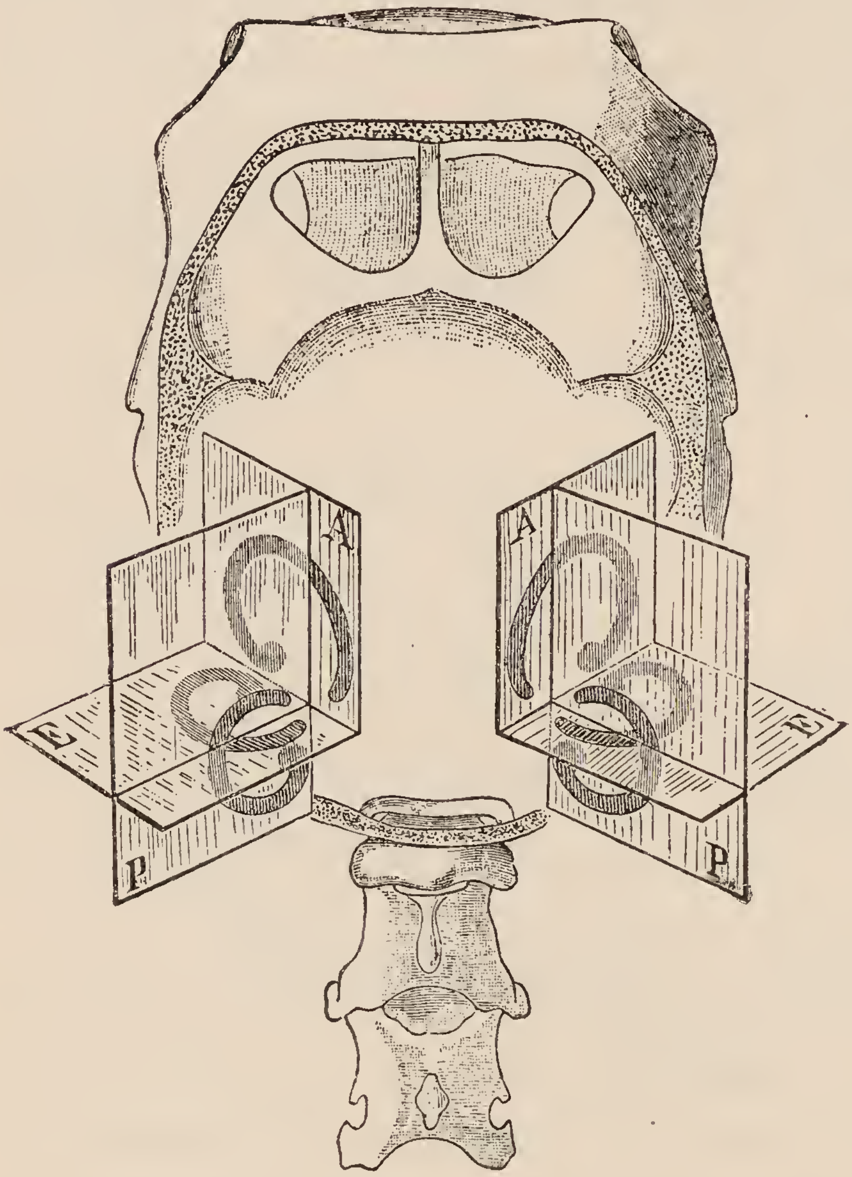


FIG. 49.—Figure from Ewald showing the situation of the three semicircular canals in the skull of the pigeon. (Starling's *Principles of Physiology*.)

A, plane of anterior or superior semicircular canal; P, plane of posterior; and E, that of horizontal canal.

Note that the anterior canal of one side and the posterior canal of the other side are in the same plane.

The bony labyrinth contains perilymph, and the membranous cavities contain endolymph; the membranous structures are attached to the bony labyrinth by fibrous strands.

The functions of the semicircular canals have been ascertained chiefly by experiments on pigeons, in which they are easily accessible. If the horizontal canals are destroyed, the head oscillates from side to side in a horizontal plane; after section of the posterior or superior vertical canals, the head and body are thrown into constant movement in a vertical plane, so that the animal tends to turn somersaults.

After destruction of all the canals, the animal is in constant violent movement, but can neither stand, walk, nor fly. After a time partial recovery takes place, but the symptoms return when the eyes are bandaged, showing that the partial recovery is due to compensatory utilisation of the visual sensations for co-ordination.

It is clear from these observations that the canals are essential

for the co-ordination of muscular movements and for the maintenance of equilibrium. Each movement of the head sets up a stimulus in one or other of the canals, which passes along the vestibular nerve to the cerebellum; these impulses serve to co-ordinate and restrain the movement. In the absence of these guiding impulses the movements become completely uncontrolled, and the sense of the position of the head is lost. The existence of three pairs of canals in three different planes makes it possible for impulses to be aroused in whatever plane the head is moved.

These impulses originate in the movements of the endolymph, which take place when the head is moved and cause the pressure on the hair cells of the cristæ to be increased or diminished. This was shown by Ewald, who connected a small tube with one canal in such a way that he was able suddenly to blow into the canal so as to cause the endolymph to flow towards the ampulla. Every time this was done, the animal moved its head and eyes in the plane of the stimulated canal and in the direction of the current.

The afferent impulses arising in the semicircular canals maintain equilibrium and muscular co-ordination, even after removal of the cerebral hemispheres. In normal circumstances, however, they also affect consciousness, and we are aware of the movements of the head. Interference with these impulses in man by disease of the canals brings about sensations of giddiness and disturbance of equilibrium.

The semicircular canals are also concerned with the maintenance of muscular tone, and more particularly with the variations in tone of different muscles according to the position of the head and body. In the rabbit, for example, when the head is raised the tone of the muscles of the forelimbs is increased, the effect being abolished by destruction of the semicircular canals.

These reflex variations of muscular tone, which are known as *postural reflexes*, play a part in the muscular adjustment of the animal to changes of position, and assist in the maintenance of equilibrium.

The maculæ acusticæ are subject to constant stimulation by the otoliths. The part of the macula upon which the otoliths exert pressure varies according to the position of the head, and the stimulation of the hair cells by the pressure of the otoliths is also variable. The impulses to which these stimuli give rise serve to give information as to the position of the head when at rest, or in progressive, as distinct from rotatory, movement.

The Muscle Sense.—Even when the eyes are closed we are conscious of the position of the body and limbs when at rest, and of movement of the limbs, whether this be active or passive. This consciousness

constitutes muscle sense, and is brought about by afferent impulses constantly passing from special structures in the muscles, joints, and ligaments. About one-third of the fibres in a nerve to a muscle are afferent in function, and do not degenerate on section of the anterior roots. These afferent fibres terminate in the muscles in neuro-muscular spindles, lying between the ordinary muscle fibres. The muscle spindles consist of fine muscular fibres surrounded by a connective-tissue sheath. A nerve fibre loses its myelin sheath, pierces the covering of the spindle, and divides into bundles of fibrils which make several spiral turns round the muscle fibres, and then end by arborisation. Other nerve endings are found in tendon, and consist in the arborisation of a nerve fibre around a bundle of tendon fibres.

Sensation of passive movements is due chiefly to impulses arising in the joints, that of active movements to impulses arising in the muscles. It is through this sense that we are able to form an estimate of weight.

The impulses giving rise to muscle sense also take part in the co-ordination of muscular movement, as has already been described; and their absence may lead to disturbances of equilibrium.

The maintenance of equilibrium is dependent, therefore, on afferent impulses from the muscles and the labyrinth as well as from the eyes and the skin; when the sensations resulting from the impulses from these different sources are discordant, we experience a feeling of giddiness, and at the same time equilibrium is disturbed.

CHAPTER VII.

THE BLOOD.

All the active cells and tissues are in intimate relationship with capillary vessels, through which blood is continually flowing. Both tissue elements and capillary are bathed with a fluid called lymph, and a constant interchange of material takes place through the lymph between the tissues and the blood. On the one hand, oxygen and other nutritive substances pass from blood to tissue to repair loss of substance, and to furnish a source of energy, and on the other hand, carbonic acid and other waste materials pass from the tissues to the blood. An exchange of water and salts also takes place through the capillary wall by diffusion. In some organs certain substances, called hormones, are supplied to the blood, and are carried in it to the glands or muscle fibres which they are destined to excite. Further, as the blood circulates, now through glands and muscles in which heat is produced, now through other structures in which heat loss occurs, it serves to equalise the temperature of the different parts of the body.

Freshly shed blood is a red, viscid, opaque fluid with a specific gravity of 1055. The specific gravity may be ascertained with a single drop of blood by making a mixture of chloroform and benzole, and finding the proportions of the two fluids in which a drop of blood remains suspended without tending either to sink or rise. The specific gravity of the mixture, ascertained by means of a hydrometer, is that of the blood itself.

When human blood is examined under the microscope, it is seen to consist of two kinds of corpuscles floating in a pale yellow fluid, the blood plasma. The corpuscles which are most numerous are the red blood corpuscles, or erythrocytes. The other variety of corpuscle, the white blood corpuscle, or leucocyte, is in the proportion of 1 to 500 red.

The *red corpuscles*, when seen singly, are yellow in colour, but when massed together they give blood its red appearance. They are circular, biconcave, non-nucleated discs, each having a diameter of 7·5 thousandths of a millimetre (7·5 μ). In all mammals except the camel tribe, the

shape of the red corpuscle is the same as that of the human erythrocyte; in camels the corpuscle is oval and biconcave.

The *white blood corpuscle* is a colourless, nucleated cell, and several varieties occur in human blood. The most abundant type, forming about 70 per cent. of the total number of leucocytes, is the *polymorphonuclear*, so called because the nucleus consists of lobes, connected by finer strands. This cell is rather larger than the erythrocyte, being about 10μ in diameter. It possesses the power of amœboid movement, and, because of its function of ingesting bacteria and foreign particles, is said to be phagocytic. Its protoplasm contains numerous fine granules which stain with neutral dyes, and are described as *neutrophile*. A somewhat similar corpuscle, in which, however, the nucleus is usually horse-shoe-shaped, contains large granules which stain deeply with acid dyes, such as eosin. These cells are called *eosinophile*. They form from 1 to 5 per cent. of the total number of leucocytes. A *basophile* variety, in which the granules stain with such basic dyes as methylene blue, is found only occasionally in normal blood. *Small and large lymphocytes* form about 25 per cent. of the total number of leucocytes, the small variety being the more numerous. Lymphocytes are distinguished by containing a large spherical nucleus surrounded by a small amount of hyaline protoplasm, which does not contain granules.

Other bodies, called *blood-platelets*, are found in recently shed blood, but these cannot be seen when precautions are taken to prevent the blood coming in contact with foreign substances; and it is believed that they are not a formed constituent of normal blood. Blood-platelets are colourless bodies, one-third to one-half the size of red corpuscles, and each contains a central group of granules resembling a nucleus. If examined on metaphosphate agar, the platelets show amœboid movement.

The blood of a healthy man contains about 5,000,000 red corpuscles in each cubic millimetre, that of a woman about 4,500,000. The corpuscles are counted by means of a hæmocytometer. This consists of a glass cell of known depth, the floor of which is ruled in squares of known size. The blood is diluted 100 times with a slightly hypotonic solution of sodium sulphate, which prevents coagulation, and the cell is filled with the mixture. The corpuscles settle on the squares and can be counted under the microscope. The volume corresponding with each square and the dilution of the blood being known, the number of corpuscles per cubic mm. of blood can be calculated. The number is diminished by hæmorrhage and in certain diseases, and is increased by living at high altitudes.

The white corpuscles number about 10,000 in each cubic millimetre of blood. They can be counted by means of the hæmocytometer, the

blood being diluted ten times with a saline solution similar to that used for red corpuscles, but containing a little methylene blue to stain the leucocytes.

THE RED BLOOD CORPUSCLES.

Each red corpuscle is soft, and alters its shape readily so that it can pass through even the narrowest capillary vessels. It is also elastic, and readily regains its shape when the compressing influence is removed. Two views are held as to the intimate structure of the erythrocyte. According to one, the corpuscle consists of a sponge-like framework (stroma) containing hæmoglobin, the blood pigment, loosely combined with the stroma. Schäfer's view, on the other hand, is that the corpuscle consists of an envelope containing the hæmoglobin in solution in its interior. Whichever view be adopted, it is clear, from the behaviour of the corpuscle in presence of reagents, that its superficial layer behaves to some extent as a semi-permeable membrane readily allowing the passage of water but not of salts. Thus, if red blood cells are placed in a fluid the salt content of which is markedly below that of blood plasma, water passes into the corpuscle and distends it, so that ultimately the membrane ruptures and the hæmoglobin is discharged. On the other hand, if the surrounding fluid is hypertonic, for example 2 per cent. NaCl, water passes out of the corpuscle, which becomes shrunken and crenated in consequence. In ·9 per cent. NaCl, which is isotonic with mammalian blood plasma, the cell is unaltered.

The envelope of the corpuscle is dissolved by weak alkalies or by ether, and this makes it probable that it is of a fatty nature. Bile salts (which are solvents of fats), amyl alcohol, soaps, higher fatty acids, and saponin or sapotoxin also dissolve the red corpuscles, setting free the hæmoglobin. The same result can be attained physically by alternate freezing and thawing. The setting free of the hæmoglobin by any of these means is called *hæmolysis.*

Certain physiological substances also bring about hæmolysis and have been termed *hæmolysins.* Snake venom, and frequently the serum from an animal of another species, act in this way. Moreover, the serum of an animal A, which is not naturally hæmolytic for the blood of another animal B, may be made hæmolytic for the blood of that animal, if A has been inoculated with blood from the species B some days before the experiment is made. Thus rabbit's red corpuscles are not broken up by the serum of a guinea-pig. If, however, rabbit's blood has been previously injected into a guinea-pig, the serum from the latter becomes hæmolytic for rabbit's red corpuscles.

Serum which is either naturally or artificially hæmolytic loses its power to dissolve red corpuscles if it is heated to 55° C. But such serum can have its hæmolytic power restored by the addition of serum from a normal animal. The hæmolytic power of any serum therefore depends upon the presence of two substances, one which is present in normal serum and is destroyed at a temperature of 55° C., and is usually called *complement*; and a second which is stable at 55° C., and may be produced in an animal by injection of the corpuscles of another animal.

Hæmoglobin may thus be set free from the erythrocytes and pass into solution in the surrounding fluid in three ways:—

(1) By a physical process, as by dilution with water or by alternate freezing and thawing.

(2) By chemical means, for example, the solution of the lipoid stroma of the corpuscles by bile salts, amyl alcohol, soaps, or other reagents.

(3) By physiological agents, called hæmolysins, the exact mode of action of which is not known.

As the result of hæmolysis by any of these methods the blood is said to be "laked." The hæmoglobin is in solution, and the blood, previously opaque on account of the reflection of light from the erythrocytes, becomes transparent.

THE CHEMICAL COMPOSITION OF RED BLOOD CORPUSCLES.

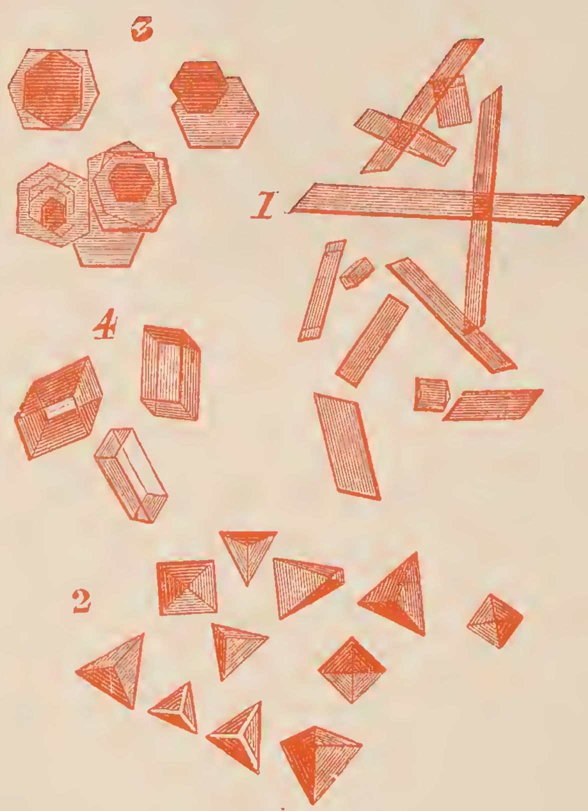


Fig. 50.—Hæmoglobin crystals, magnified. (From Quain's *Anatomy.*)

1, from human blood; 2, from the guinea-pig; 3, squirrel; 4, hamster.

The red corpuscles may be obtained in sufficient quantity for analysis by centrifugalising blood and washing the deposit with ·9 per cent. NaCl. They are found to consist of 63·3 per cent. of water and 36·7 per cent. of solids. Hæmoglobin forms 95 per cent. of the dry solids, the remainder being made up of nucleoprotein, lecithin, cholesterol, fatty acid, and inorganic salts, the most abundant of the latter being potassium phosphate. The stroma is, therefore, as has already been pointed out, largely of a lipoid nature.

Hæmoglobin is a compound of globin, which is a protein belonging to the group of histones, with an

iron-containing substance, hæmatin. The molecule of hæmoglobin is a very large one, and its formula is given by one authority as $C_{758}H_{1203}N_{195}S_3FeO_{218}$. Although it is a colloid, hæmoglobin crystallises fairly readily. The crystals vary in shape in different animals, but in all cases they belong to the rhombic system. In man they are rhombic prisms, in guinea-pigs they form tetrahedra (fig. 50). Hæmoglobin is purple in colour, is soluble in water, and its solutions, examined with the spectroscope, show a broad absorption band in the green between Frauenhofer's lines D and E (fig. 51, sp. 2).

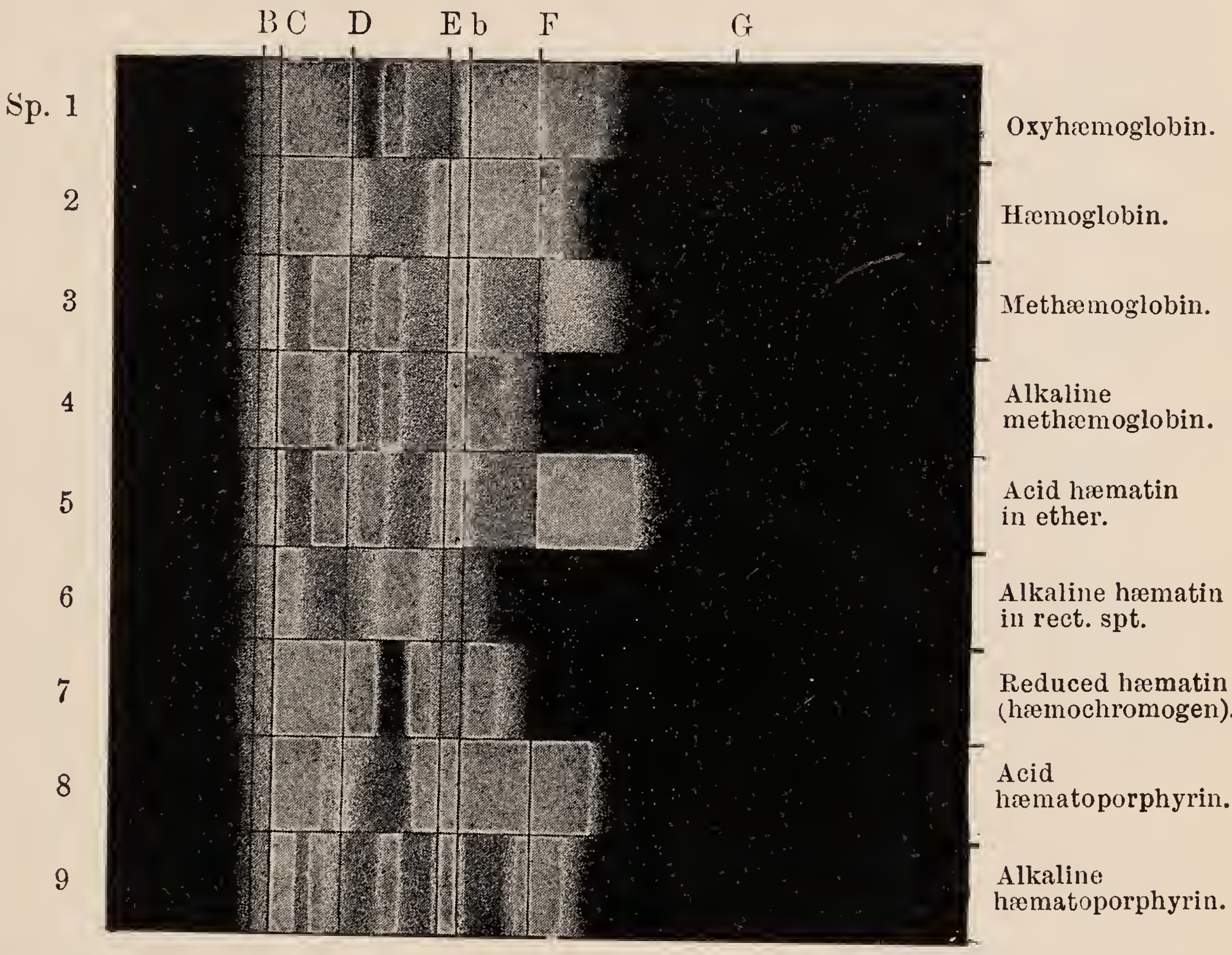


FIG. 51.—Spectra of hæmoglobin and its derivatives. (From Mac Munn's *Spectrum Analysis.*)

The most important property of hæmoglobin is its affinity for oxygen, each molecule combining with two atoms of oxygen to form oxyhæmoglobin. The combination is a loose one, for the attached oxygen is given up if the solution containing the compound be exposed to a vacuum, or if a reducing agent, such as ammonium sulphide, be added to it, HbO_2 (oxyhæmoglobin) again becoming Hb (hæmoglobin). In the living body the same reduction takes place as the blood circulates through the capillaries of the active tissues. Oxyhæmoglobin is characterised by a scarlet colour, and its spectrum exhibits two absorption bands in the green, between the D and E lines (fig. 51).

The oxygen-carrying power of hæmoglobin depends upon hæmatin

the prosthetic group of the molecule, and the value of hæmatin in this respect is determined by the presence of iron. The actual amount of iron is small. Hæmatin forms about 4 per cent. of the hæmoglobin molecule, and iron accounts for about 11 per cent. of the hæmatin, or about 0·05 per cent. of blood itself. Iron has on this account been described as the gold currency of the body, and it is carefully preserved. Red corpuscles are being continually destroyed in the liver, and the broken-down material is excreted to a large extent in the bile. Hæmatin appears in the bile in an iron-free form as bilirubin, the primary bile pigment, the iron being retained by the liver cells. The iron is eventually used in the formation of new erythrocytes, this taking place in the red marrow.

Owing to the high atomic weight of iron, the transport of a substance like hæmatin would be attended with difficulty if it were not combined with a large protein molecule. By means of its combination with globin the weight of the iron is distributed, and the resulting compound can be floated along in the blood stream without difficulty.

Hæmoglobin has an affinity for carbon monoxide 130 times as great as its affinity for oxygen, and when it is exposed to air containing even a minute quantity of the former gas, it forms with it a stable compound, *carboxyhæmoglobin* (HbCO). HbCO differs slightly in colour from HbO_2, strong solutions having a more florid appearance, and weak solutions retaining a pink colour, whereas the same dilution of HbO_2 has a yellow tinge. Solutions of HbCO, when examined spectroscopically, exhibit two bands in the green, slightly nearer the violet end than those presented by HbO_2. HbCO is unaffected by the addition of ammonium sulphide.

Hæmoglobin forms a still more stable compound with nitric oxide, HbNO, but this is purely a laboratory product, and is only of theoretical interest.

When a solution of oxyhæmoglobin is treated with ferricyanide of potassium, a volume of oxygen is given off corresponding with the dissociable oxygen of the oxyhæmoglobin molecule, and the solution becomes brown, its spectrum showing a characteristic band in the red in addition to other bands (fig. 51). The brown substance is called *methæmoglobin.* It contains the same amount of oxygen as oxyhæmoglobin, but more firmly combined, and attached in all probability to a different part of the molecule. Haldane suggests that in the case of oxyhæmoglobin the dissociable oxygen is in the molecular form $Hb\left<\begin{array}{l}O\\ |\\ O\end{array}\right.$ and in methæmo-

globin the same oxygen is combined as two separate atoms, $Hb\begin{smallmatrix}\diagup O\\ \diagdown O\end{smallmatrix}$. The addition of potassium ferricyanide to a solution of oxyhæmoglobin probably leads to the removal of the dissociable oxygen, and then re-oxidises the hæmoglobin into the more stable form of methæmoglobin.

When ammonium sulphide is added to a solution of methæmoglobin, the colour changes to red and later to purple. The intermediate red stage gives a spectrum corresponding with that of oxyhæmoglobin, the purple product is hæmoglobin, and this yields oxyhæmoglobin when it is shaken with air. By means of hydrazine hydrate it can be shown that methæmoglobin contains less dissociable oxygen than oxyhæmoglobin. The latter compound, when treated with hydrazine, gives off a volume of nitrogen corresponding with the volume of dissociable oxygen.

$$HbO_2 + N_2H_4 \cdot H_2O = N_2 + 3H_2O + Hb.$$

When methæmoglobin is treated in the same way it never yields more than half the amount of gas given off from a similar weight of oxyhæmoglobin (Buckmaster). The explanation of this fact is still obscure.

If a solution of hæmoglobin (or oxyhæmoglobin) is warmed with an acid or an alkali, the globin is converted into metaprotein, and *hæmatin* is set free. In the pure condition hæmatin is a dark brown or black amorphous substance, insoluble in water, soluble in acids or alkalies. In acid solution its spectrum shows, besides other absorption bands, a characteristic band in the red, nearer the red end of the spectrum than that given by methæmoglobin (fig. 51). The spectrum of the alkaline solution exhibits a rather faint band just to the red side of the D line. On the addition of ammonium sulphide, alkali hæmatin is converted into reduced alkali hæmatin or *hæmochromogen*, the spectrum of which shows two absorption bands in the green, some distance to the violet side of the D line, the band nearer D being the more distinct of the two (fig. 51). As these bands can be seen in extremely dilute solutions, the formation of hæmochromogen constitutes a delicate spectroscopic test for blood pigment.

As has already been said, hæmatin contains the iron of the Hb molecule, and it has had the formula $C_{34}H_{34}N_4FeO_5$ assigned to it. It forms a compound with hydrochloric acid, hydrochloride of hæmatin or *hæmin*, which is easily obtained by heating blood with glacial acetic acid in the presence of sodium chloride. Hæmin occurs in dark brown rhombic crystals (fig. 52), and its formation is utilised as a medico-legal test for blood. In the reduced condition, hæmatin will recombine with globin to form hæmoglobin or a substance indistinguishable from

hæmoglobin, provided the globin has not been destroyed by the reagents used to dissociate the hæmoglobin molecule.

If hæmatin (or hæmoglobin) be treated with a strong mineral acid, iron-free hæmatin or *hæmatoporphyrin*, $C_{34}H_{38}N_4O_6$, is formed. Acid solutions of this substance show a spectrum with two absorption bands, one on either side of the D line, that to the red side being the narrower (fig. 51). The spectrum of alkaline solutions is somewhat similar to that of methæmoglobin (fig. 51). Hæmatoporphyrin occurs occasionally in the urine in sulphonal poisoning, its spectrum in such cases being of the alkaline type. Two similar substances are found in the body, *hæmatoidin* in old blood clots, and *bilirubin*, the primary bile pigment; they are formed from hæmoglobin and are said to be identical, each containing one atom less of oxygen than does hæmatoporphyrin.

FIG. 52.—Hæmin crystals, magnified. (Preyer.) From Quain's *Anatomy*.

THE ESTIMATION OF HÆMOGLOBIN.

The estimation of the amount of hæmoglobin contained in a sample of blood is usually carried out by a colorimetric method. The apparatus used is called a hæmoglobinometer, and consists of two tubes, one of which is sealed and contains a standard dilution of ox blood, the hæmoglobin of which has been converted into carboxyhæmoglobin. A little distilled water and a measured quantity of the blood to be examined are placed in the second tube, which is graduated. The blood, laked by the water, is exposed to coal gas, and in this way the hæmoglobin is converted into carboxyhæmoglobin. It is then diluted with distilled water till the tints of the two tubes are alike, and the level of the fluid in the graduated tube is read. If the latter is at the figure 100, the amount of hæmoglobin is said to be normal or 100 per cent. If it is over 100, the blood is abnormally rich in hæmoglobin; if below 100, it is deficient in hæmoglobin. The figure 100 per cent. is purely empirical, and the amount of hæmoglobin actually present in blood is normally about 14 per cent.

If the number of red corpuscles in the blood is ascertained at the same time, the value of the hæmoglobin content of each corpuscle can be stated. Thus if the number of corpuscles is the normal five millions per cubic

millimetre and the hæmoglobinometer gives a reading of 50 per cent., each corpuscle only contains half the normal amount of hæmoglobin.

THE ORIGIN AND FATE OF RED BLOOD CORPUSCLES.

(1) *In early embryonic life* red blood corpuscles are formed in areas, known as "blood-islands," lying in the *area vasculosa* of the blastoderm. The blood-islands lie between the mesoderm and the entoderm, and are said to be derived from the latter. They consist of branched cells which unite to form a syncytium, their nuclei mean-

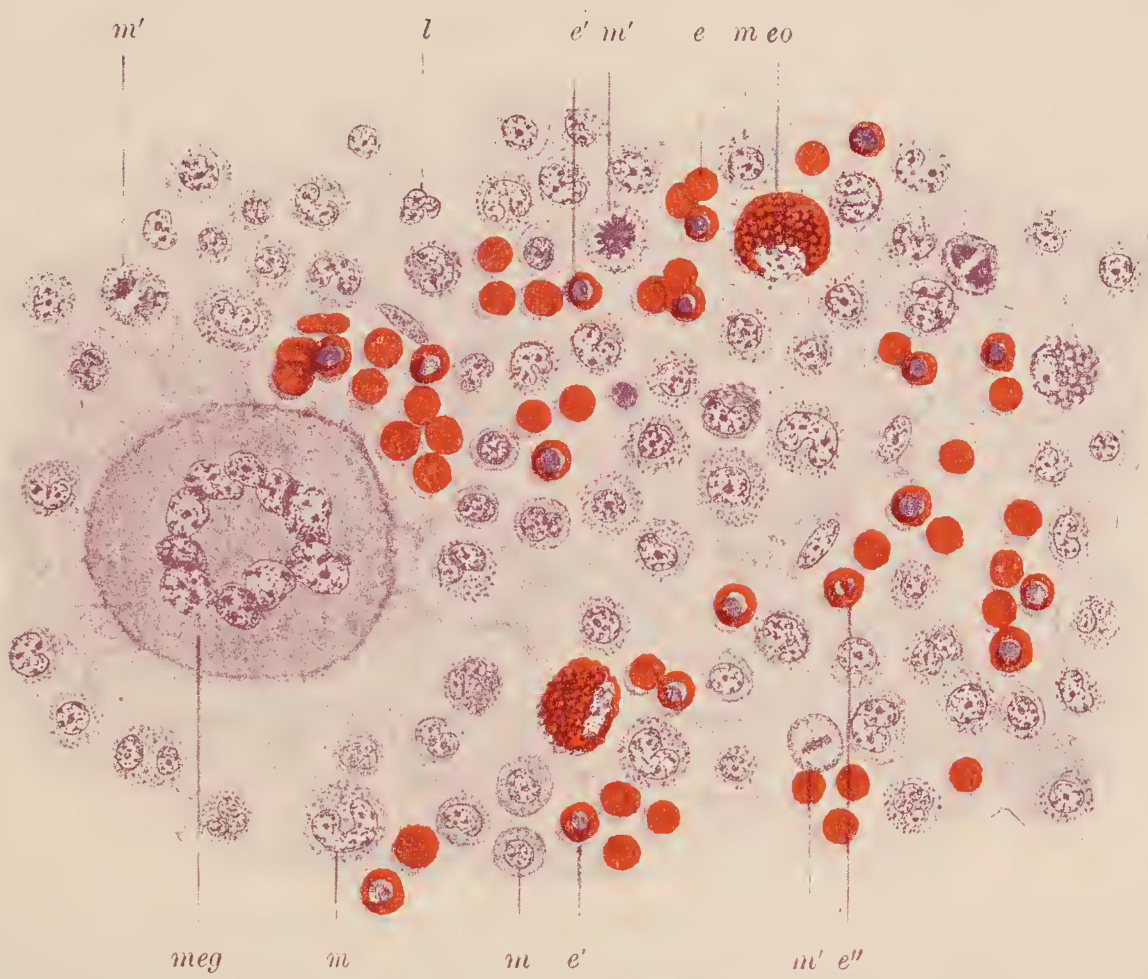


FIG. 53.—Red marrow of young rabbit. Magnified 450 diameters. (From Schäfer's *Essentials of Histology.*)

e, erythrocytes; *e'*, erythroblasts; *e''*, a coloured cell undergoing mitotic division; *l*, a polymorphonuclear leucocyte; *m*, ordinary myelocytes; *m'*, myelocytes undergoing mitotic division; *eo*, an eosinophile myelocyte; *meg*, a giant-cell or megakaryocyte.

while dividing and each new nucleus becoming surrounded by protoplasm containing hæmoglobin. The coloured cells thus formed are known as erythroblasts, and are the red corpuscles of the embryo. They multiply by division. *In later embryonic life* similar nucleated coloured cells, or erythroblasts, are found undergoing division in the sinus-like blood-vessels of the liver, and also in the pulp of the spleen. Non-nucleated erythrocytes, like those developed in post-natal life, are formed in the embryo in connective tissue. The connective-tissue cells become coloured by the formation of hæmoglobin, and the coloured protoplasm is subdivided into a number of discs, or erythrocytes, which

lie free in the hollowed interior of the cell. Adjacent cells have meanwhile become united to form a syncytium, and the hollows become continuous along the connecting branches, so that a system of blood-vessels is formed.

(2) *In post-natal life* nucleated red corpuscles or erythroblasts are found in the red marrow of bone (fig. 53). These are constantly undergoing mitotic division; the cells thus formed lose their nuclei by atrophy or extrusion and pass into the blood capillaries, which in the marrow probably have incomplete walls. Nucleated red corpuscles may pass into the blood stream after birth in certain diseases in which a rapid destruction of blood corpuscles is taking place.

The duration of the existence of a single red corpuscle is not known, but there is evidence that large numbers of these cells are destroyed daily to form the pigment of the bile. Fragments of broken-down erythrocytes are also of constant occurrence in the cells of the spleen. Moreover, the pigment of hair and of the coloured parts of the skin is believed to be derived from hæmoglobin. Blood corpuscles are also lost by accidental hæmorrhage, in disease, and, in the female, by menstruation. The deficiency brought about in all these ways, normal or abnormal, is as a rule rapidly and completely made good by the activity of the bone marrow, which, in post-natal life, is the only source of the red corpuscles. When an unusually large and rapid formation of red corpuscles is required, for instance after severe hæmorrhage, the red marrow increases in amount, and replaces the yellow marrow to some extent.

THE WHITE BLOOD CORPUSCLES.

The distinguishing feature of the polymorphonuclear leucocytes is their power of amœboid movement, a power which is shared by the eosinophile cells, and to a much less extent by the lymphocytes. The leucocytes are able to make their way through the capillary walls between the epithelial cells and wander out into the tissue fluids of the body. They are especially susceptible to certain chemical stimuli (*chemiotaxis*), and are found to concentrate in large numbers round various chemical substances placed in their neighbourhood. For example, they appear in force where pathogenic bacteria are active, and serve a useful purpose in surrounding and destroying these germs, and thus constitute an important protective mechanism for the body. When the leucocytes fail to overcome and ingest the bacteria, they may themselves be destroyed by the bacterial toxins. The same function of the removal of useless or harmful material is shown in other ways. For example, the removal of the tail of the tadpole is effected by leucocytes,

and in the mammalian body dead cells and organic foreign substances, such as buried catgut ligatures, are ingested by the same cells. On account of this property of "eating up" bacteria and dead matter, polymorphonuclear leucocytes are included under the term *phagocytes.*

The leucocytes consist largely of proteins, cell-albumin, cell-globulin, and nucleo-protein; they also contain a little glycogen, with some neutral fats, and lecithin and cholesterol. The inorganic salt which is most abundant in their composition is, as in the case of the red corpuscles, potassium phosphate.

In the embryo leucocytes are derived from cells which resemble the erythroblasts but are colourless. In post-natal life the polynuclear and eosinophile cells, as also the basophile cells when they occur, are derived from the special cells of red bone marrow called myelocytes; the lymphocytes are derived from lymph glands and lymphoid tissue generally, including that of the Malpighian bodies of the spleen. The nuclear changes which accompany cell division can be seen in definite areas, known as germ centres, in the lymphoid tissue of the lymphatic glands and elsewhere.

The condition called *leucocytosis*, or increase of the number of leucocytes in the blood, occurs normally during the digestion of a protein meal. It also takes place in many infective diseases, being accompanied by overgrowth of the red marrow, in which the polymorphonuclear cells are formed. The increase in the number of polymorphonuclear leucocytes in the blood is part of the process by which the body resists and overcomes infection by micro-organisms.

THE BLOOD PLASMA.

When blood is shed, it rapidly becomes viscid and in a few minutes sets to form a clot. It is therefore necessary to use means to retard or prevent clotting in order to obtain plasma for examination and analysis. The various methods which are used for this purpose will be described in connection with coagulation.

Plasma is a pale yellow fluid, and has a specific gravity of about 1030, considerably lower than that of blood as a whole. The red corpuscles have a specific gravity of about 1090, and therefore sink if blood which is prevented from coagulating is allowed to stand. It is found that the proportion of H and OH ions in plasma or blood is about equal, and therefore its reaction is neutral. It must be noted, however, that although blood gives a neutral reaction with phenolphthalein, it is alkaline to litmus, because litmus acid is strong enough to displace the acid from sodium bicarbonate, which is an important constituent of plasma, and to combine with the sodium.

On analysis, plasma is found to contain a large number of substances, some of which, particularly fibrinogen, appear to be essential constituents of the plasma itself, some are food stuffs being conveyed to the tissues, some are waste products being carried to excretory organs, and others are hormones, enzymes, and bodies of like nature. A list of the principal constituents is given in the following table :—

The Composition of Blood Plasma.

Water, 92 per cent.

Proteins—serum albumin, serum globulin, fibrinogen—6 to 8 per cent.

Dextrose, 0·15 per cent.

Neutral fats.

Urea (0·02 to 0·05 per cent.), lecithin, cholesterol, lactic acid, and other bodies.

Hormones.

Enzymes—lipase, etc.

Inorganic salts—chlorides, sulphates, phosphates, and carbonates of sodium, potassium, calcium, magnesium, and iron.

Pigment and aromatic substances.

Gases—oxygen, carbonic acid, and nitrogen.

The Proteins of Plasma.—If an equal volume of a saturated solution of sodium chloride is added to plasma, and the mixture is allowed to stand, a sticky white precipitate separates out, consisting of *fibrinogen.* This substance is a globulin, and the precipitate may be dissolved in weak salt solution. Fibrinogen exists in much smaller quantity than the other proteins, forming about 0·3 per cent. of the plasma. If plasma is allowed to clot, a comparatively insoluble, stringy substance called fibrin is formed, and, if this is removed, the fluid which remains is plasma minus fibrinogen, and is called serum.

When serum is treated with an equal volume of a saturated solution of ammonium sulphate, a precipitate of *serum globulin* is obtained. This precipitate is found to be a mixture of two substances, one of which, euglobulin, is a true globulin, while the other, pseudo-globulin, resembles albumin in being soluble in distilled water. If serum from which serum globulin has been removed is saturated with ammonium sulphate, a further precipitate of *serum albumin* is obtained. The filtrate from this contains no other protein. Fibrinogen coagulates at about 56° C., serum globulin at 75°, and serum albumin at a slightly higher temperature.

Although albumin and globulin can be separated from serum by chemical methods, there is reason to believe that in the serum itself these two substances are combined to form one—*serum protein.*

The Osmotic Pressure of Blood Plasma.—It has already been pointed out that the osmotic pressure of the plasma is the same as that of the corpuscles, so that it is also the same as that of the blood as a whole. It has been found by experiment that the proteins of plasma have a slight osmotic pressure, but the osmotic pressure is chiefly due to the inorganic salts. One method of ascertaining the osmotic pressure of blood is to determine how much lower its freezing point is than that of water, and in the case of blood it is found to be 0·56° C., which is equivalent to that of a 0·9 per cent. solution of sodium chloride.

If the osmotic pressure of the blood is higher than that of the tissues, water will pass from the tissues into the blood in the capillaries, and salts will diffuse from the blood into the tissues. If the osmotic pressure of the blood is lower than that of the tissues, the reverse processes will occur, water passing from blood to tissues, and salts from tissues to blood. This interchange is an important factor in the maintenance of the balance between the intake and output of water and salts.

PROTECTIVE AND OTHER SUBSTANCES IN THE PLASMA.

A large number of substances, when introduced under the skin or directly into the circulation (but not when given by the mouth), give rise to the formation by the tissues and the setting free in the blood-stream of products which tend to destroy or to precipitate the substance introduced, or to neutralise its action. The products thus formed are called *antibodies*, those which excite their formation being called *antigens*. Antigens are colloidal, and almost any protein, including harmless bodies such as egg-white and caseinogen, can act as an antigen. Crystalloid substances of small molecular weight, such as sugar, seem unable to give rise to antibodies.

If a little human blood serum is injected into a rabbit on several occasions at intervals of a week, the blood serum of the rabbit acquires the power, when tested *in vitro*, of precipitating the proteins of human serum, but not those of the serum of other animals. The substance thus formed in the rabbit's blood is called a *precipitin*. If the rabbit is injected with sheep's serum, the precipitin formed will precipitate sheep's serum *in vitro*, but not that of any other animal. The precipitin acts, therefore, only on the serum of an animal of the same species as that from which blood is taken for injection into the rabbit; and the reaction is said to be *specific*. Since this reaction is not only one of the most delicate known tests for the presence of blood, but also makes it possible to ascertain the species of animal from which the blood was

derived, it has been used in medico-legal cases to ascertain whether blood, for example on clothes or weapons, is of human origin or not.

Again, the poisons (toxins) formed by bacteria give rise, when introduced into the body, to antibodies which neutralise the toxin. If, for example, a minute amount of diphtheria toxin is injected at intervals into an animal, the latter forms *antitoxin* in considerable amount. This antitoxin is able to neutralise diphtheria toxin, and such an animal will now survive the injection of a huge dose of toxin, many times larger than that which would previously have killed it; and it is said to be *immune* to that toxin. In this example the toxin and antitoxin combine directly with one another. In other cases, however, the antibody which is formed does not itself destroy the antigen, but forms a link between the antigen and a substance present in normal serum and known as *complement*; the complement, thus linked on to the antigen, is able to destroy it. Antigens of this kind include bacteria, red blood corpuscles and tissue cells, and the antibodies are called *lysins*. The formation of *hæmolysin* (p. 157) is an example of this process.

The capacity to form antibodies, which can destroy or neutralise bacteria and their toxins, is one of the fundamental means by which human beings are enabled to resist or to recover from diseases of bacterial origin.

Anaphylaxis.—If a small dose of an antigen, such as egg-white, is injected into an animal, and after an interval of sixteen days or more, a second, even smaller dose is given, the animal becomes extremely ill and may die in a few minutes. In guinea-pigs, which are particularly sensitive, there is a marked fall of blood pressure, extreme constriction of the bronchioles, and convulsions. This hypersensitiveness of an animal to a second dose of an antigen is known as *anaphylaxis*.

The Reaction of the Blood.—The acid characters of a substance such as hydrochloric acid in solution are due to the presence in it of free hydrogen ions (H ions); similarly the alkaline characters of an alkali such as caustic potash depend upon the presence of free hydroxyl ions (OH ions). In a perfectly neutral solution, the two kinds of ions are present in equal amount. In any aqueous solution, whatever its reaction, the product of the proportion of H and OH ions present is a constant figure, but in an acid solution the H ions will be in excess, whereas in an alkaline solution they will be relatively few as compared with the OH ions. It is customary to express the reaction of a fluid in terms of its concentration in H ions, this being indicated by the formula C_H. In an acid solution the relative concentration of H ions is large, whereas in an alkaline solution it is small.

The reaction of blood to litmus is alkaline, but when it is determined accurately in terms of H ion concentration, it is found to be almost the same as that of distilled water. Under various conditions the reaction may alter slightly, and these changes produce marked physiological effects in the body, although they are usually too slight to affect an ordinary indicator, such as litmus. Further, the presence in blood of proteins and phosphates makes it possible for a considerable amount of acid or alkali to be added to blood without any appreciable change being produced in the H ion concentration. The reason is that the acid or alkali thus added combines with proteins or phosphates to form compounds which do not undergo ionic dissociation, and therefore does not alter the concentration of H ions, by which the reaction of the blood is ultimately determined. For example, Na_2HPO_4 can be partly converted into NaH_2PO_4 on the addition of acid, with little or no alteration in the number of free H ions present in the solution.

THE COAGULATION OF THE BLOOD.

When blood is shed, it becomes more viscid, and within three to ten minutes it begins to set into a jelly-like clot. The clot gradually contracts, expressing a yellow fluid, the serum, as it does so; and within ten to forty-eight hours the process results in a shrunken, firm clot floating in the expressed serum. If coagulation has taken place slowly, so that the corpuscles have had time to settle, the upper part of the clot will be paler than the deeper part, because the lighter leucocytes do not sink so quickly as the heavier red cells.

If a drop of blood be placed on a slide and covered with a cover-slip, the process of clotting may be observed microscopically. It is found that the red corpuscles become aggregated into rouleaux, and that between the aggregations delicate threads of fibrin make their appearance. Clotting thus consists in the formation of a meshwork of threads of fibrin, entangling the corpuscles; and the subsequent shrinking of the clot is due to the contraction of the newly formed fibres.

Fibrin may be obtained in quantity by whipping a large volume of freshly shed blood with a bundle of twigs, when the fibrin adheres to the twigs as it forms. Blood treated in this way will not clot subsequently, and is spoken of as defibrinated blood. The fibrin, when washed free of blood pigment, is a white, stringy substance, easily stretched and possessing considerable elasticity. It is insoluble in water and in dilute salt solutions, but dissolves slowly in 5 per cent. sodium chloride. It swells up and slowly dissolves in 0·2 or 0·4 per cent. hydrochloric acid, with the formation of acid metaprotein.

The essential change in the coagulation of blood is the conversion of fibrinogen into fibrin. The former substance is no longer present in defibrinated blood or in serum. The process of clotting may therefore be represented diagrammatically in this way:

$$\begin{tikzcd}
\text{Plasma} \arrow[dd] \arrow[dr] & & \text{Corpuscles} \arrow[dd] \\
& \text{Fibrin} \arrow[dr] & \\
\text{Serum} & & \text{Clot.}
\end{tikzcd}$$

When fibrinogen is freed from other substances by repeated precipitation, a solution of the pure substance is found to have lost the property of spontaneous coagulation. If, however, some blood serum is added to such a pure solution, clotting will occur. It is clear, therefore, that at least two substances are necessary for the formation of fibrin, and that one of these is contained in blood serum. If twenty volumes of alcohol are added to one volume of serum, a precipitate of serum proteins is formed, and becomes insoluble in water if allowed to remain under alcohol for some days or weeks. If this precipitate be then dried and extracted with water, the solution so obtained will, if added to a solution of fibrinogen, cause the latter to clot. The watery extract contains a substance of unknown composition, which has been called *thrombin.*

We therefore find that the formation of fibrin is due to the interaction of fibrinogen and thrombin; and, further, it has been shown that a combination of the two bodies takes place, because, if excess of fibrinogen be present, the amount of fibrin formed is proportional to the amount of thrombin added to it. This latter fact is opposed to the theory formerly held that thrombin belongs to the group of ferments. The untenability of the older theory is further shown by the discovery that the activity of thrombin is not permanently destroyed by the action of heat. Moreover, fibrin can be partly broken down, thrombin being set free, by treating it for some time with 8 per cent. sodium chloride solution.

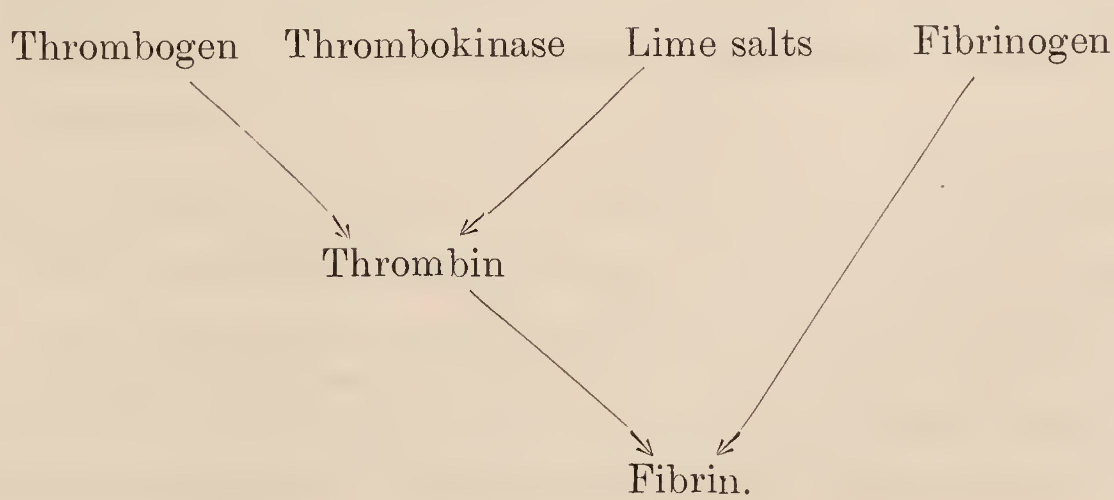
Thrombin itself is not contained in the blood-stream of the living animal. If blood is drawn directly from a blood-vessel into alcohol, it contains no thrombin, so that the latter body must be produced after the blood is shed. It has, in fact, been shown that it is derived from a precursor, which has been called *thrombogen*, by the combination of the latter substance with calcium salts. If freshly shed blood is

mixed with potassium oxalate solution in such quantity that the mixture contains 0·1 per cent. of potassium oxalate, the calcium salts of the plasma are precipitated as calcium oxalate, and the blood will not clot. The subsequent addition of calcium chloride is followed by coagulation. But if oxalate serum is added to oxalate blood, clotting will take place, because thrombin is already present in the serum before the potassium oxalate is added.

The formation of thrombin from thrombogen and calcium salts is brought about, or at least facilitated, by an activating substance called *thrombokinase*, which is derived in mammals mainly from the blood platelets. If oxalate plasma from a mammal is allowed to stand for two or three days on ice, a precipitate of platelets collects at the bottom of the vessel. The plasma still contains thrombogen, but will no longer coagulate on the addition of lime salts. It will clot, however, if some of the platelet precipitate or an extract of an animal tissue be added to it along with the lime salts, the extra factor, obtained from the platelets or tissues, being thrombokinase. Again, the blood of birds contains no platelets, and will not clot if it is drawn directly from a blood-vessel without contact with the tissues. On the other hand, if it is allowed to flow over the adjacent tissues on its passage from the vessel, or if a little tissue extract is added to it, it will coagulate readily. Thrombokinase is therefore present in nearly all the tissues of the body as well as in the platelets, and this wide distribution facilitates the protective clotting of the blood which takes place on wounded surfaces. The leucocytes have also been supposed to discharge thrombokinase when blood is shed.

The facts described above in connection with the subject of the coagulation of the blood are generally accepted, but the exact interpretation of them put forward by different authors, as well as the nomenclature applied to the different substances concerned, varies somewhat.

The factors concerned in coagulation may be diagrammatically summarised as in the following table:—



Thrombogen, lime salts, and fibrinogen exist normally in blood. When blood is shed, thrombokinase, derived from blood platelets or from the tissues, brings about the combination of thrombogen and lime salts to form thrombin; thrombin then combines quantitatively with fibrinogen to form fibrin.

The Nature of Thrombin.—For many years thrombin was believed to belong to the group of ferments, but it has been shown (1) that it is not destroyed by boiling, and (2) that the amount of fibrin formed is in proportion to the amount of thrombin present. (1) Thrombin in watery solution is not affected by boiling, but thrombin contained in serum is inactivated by boiling. The inactivated substance in the latter case, however, is reactivated by the addition of alkali. The destruction of a ferment, on the other hand, at a temperature of 100° C. is one of its most characteristic features. (2) It is also characteristic of a ferment that, if the products of its activity be removed, it will in time act upon all the substrate which is present. Thrombin, on the other hand, is used up in the formation of fibrin, so that if there is an excess of fibrinogen the surplus remains unchanged, unless fresh thrombin is added.

If serum is allowed to stand for two or three days, the thrombin contained in it disappears, being converted into a substance which has been called *metathrombin*, and which can be reactivated by the addition of either acids or alkalies, with subsequent neutralisation, or by the occurrence of putrefaction. The same agencies, that is acids, alkalies, or putrefaction, will break up fibrin, yielding thrombin.

The fact that blood does not clot in the vessels must be due to one of two things: either an essential factor for coagulation is not present, or clotting is prevented by some agent which inhibits the process. With regard to the former possibility, fibrinogen exists in normal blood, calcium salts are undoubtedly present, and thrombogen must be a constituent of the blood in some form. If it be accepted that platelets are only formed when blood comes into contact with foreign matter, it would appear that the immediate precursor of thrombokinase is not in existence in the circulating blood. This has already been shown to be the case in birds, the blood of which contains no platelets. There is, therefore, good ground for believing that the circulating blood contains little or no thrombokinase. As regards the second possibility, evidence has been brought forward by some observers to show that a substance, *anticoagulin* or *antithrombin*, is a normal constituent of blood, and that it is formed in the liver. It is stated, for example, that the injection of thrombokinase or of thrombin into a blood-vessel results in the production of such an antibody, so that the blood becomes deficient

in coagulating power, just as a precipitin is produced as the result of the injection of foreign protein. Hence it has been inferred that small quantities of thrombin are continually being produced in the blood, thrombokinase being set free by the breaking down of white blood corpuscles and of the tissues generally. The presence of thrombin leads to the formation of antithrombin in the liver, and in this way clotting in the blood-vessels is prevented.

Conditions which Accelerate Clotting.—The rate of coagulation is accelerated (1) by a certain degree of warmth, (2) by agitation of the blood, and (3) by increasing the extent of the foreign surface with which the blood is in contact. A practical application of the latter fact may be made by applying a sponge or cotton wool to a bleeding surface to aid in the arrest of hæmorrhage. It is probable that the foreign surface facilitates the formation and disintegration of platelets with consequent increased production of thrombokinase.

Intravascular Clotting.—The rapid injection into the blood-stream of an animal of a quantity of a saline extract of such a cellular organ as the thymus or a lymph gland, leads to the coagulation of the blood throughout the whole vascular system. This result is generally ascribed to the presence of nucleo-protein in the extract. Small quantities of a similar extract, slowly injected, have an opposite effect, rendering the blood incoagulable. The difference in the results, according to the quantity of extract injected, has not been satisfactorily explained. Intravascular clotting is also produced by the injection of thrombokinase or of snake venom, but not by moderate quantities of thrombin.

Conditions which Retard or Prevent Clotting.—These may be classified as—

(1) Prevention of contact with a foreign surface.

(2) Removal of one or more of the substances concerned in the formation of fibrin.

(3) Interference with the interaction of the substances concerned in the formation of fibrin.

(4) The use of an anticoagulin, or the production of antithrombin by the injection of certain substances into the blood-stream before the blood is shed.

(1) Coagulation is delayed if blood is shed into a vessel the interior of which is smeared with grease of any kind. It is delayed for a longer time if the blood is kept in contact with the lining of a blood-vessel. If a large vein containing blood is ligatured in two places and the ligatured portion is excised, the blood in the vein, which is then known as a "living test-tube," may remain fluid for days.

(2) (*a*) Lime salts are precipitated by the addition of potassium

oxalate or of sodium fluoride to blood. (*b*) Sodium fluoride precipitates not only calcium but also thrombogen, so that fluoride blood will not clot on the subsequent addition of lime salts. (*c*) If one volume of saturated solution of magnesium sulphate be added to four volumes of blood, and the mixture be allowed to stand for twenty-four hours, the thrombokinase is precipitated, and clotting will not take place on dilution. For the first few hours after the addition of the sulphate the clotting is merely retarded by the excess of salt, and the blood will clot if it is diluted. (*d*) Sodium citrate may also be used to prevent coagulation. It forms with calcium a double salt, calcium sodium citrate, which is soluble, and in which the calcium is combined with the acidic radical and does not become a free ion. Calcium will not combine with thrombogen unless it is in the ionised condition.

(3) (*a*) Coagulation may be prevented by cooling freshly shed blood to 0° C. (*b*) The addition to the blood of an equal volume of saturated solution of sodium sulphate will prevent or delay clotting, but coagulation will take place when the mixture is diluted, showing that the action of the salt is purely mechanical.

(4) Hirudin, a substance obtained by extracting the glands in the head of the leech, is an anticoagulin, and will prevent clotting either if added to shed blood or if previously injected into a blood-vessel. The injection of peptone will render blood incoagulable, and such blood, when added to blood shed in the ordinary way, will prevent coagulation of the latter; but peptone itself has no retarding effect on coagulation when added to shed blood. From experiments such as these it is clear that peptone has no direct action in preventing coagulation, but that it leads to the production in the liver of an anticoagulin, which is discharged into the circulating blood.

Coagulation Time.—The time taken for coagulation of a sample of blood may be conveniently estimated by means of Dale and Laidlaw's coagulometer. This consists of a short capillary tube containing a leaden shot. The finger is pricked and blood is run into the tube, which is then immersed in water at a selected temperature, the ends of the tube being closed. The tube is moved so as to keep the shot rolling until the latter stops dead with the tube vertical. The time between the appearance of blood on the finger and the stopping of the shot is the coagulation time. It varies from one and a half minutes at 40° C. to about eight minutes at 19° C. for normal blood.

THE TOTAL QUANTITY OF BLOOD IN THE BODY.

The amount of blood in the body of an animal is ascertained by collecting and measuring the blood obtained by bleeding the animal. To the total thus obtained must be added the blood which does not escape when the animal is bled. This must be dissolved out of the tissues until no more colour is obtained; the tint of the mixed washings is compared with that of a known dilution of the blood, and in this way the amount of dissolved blood is calculated and added to that found by direct measurement. Two experiments of this kind have been performed on the bodies of guillotined criminals, and from these it was found that the blood in man forms one-thirteenth of the body weight.

Haldane has devised a method for ascertaining the quantity of blood in the living subject. This method is based upon the affinity of hæmoglobin for carbon monoxide. A small quantity of blood is withdrawn and its oxygen capacity is estimated. The subject is then allowed to breathe air containing a known amount of carbon monoxide, which is absorbed by the blood. A certain proportion of the hæmoglobin of the blood combines with the carbon monoxide, forming carboxyhæmoglobin, and thus reducing the oxygen capacity of the blood to that extent. A small quantity of blood is again withdrawn and its oxygen capacity estimated. If it is found in this way that 100 grams of blood contain $\frac{1}{30}$ of the absorbed carbon monoxide, then 100 grams obviously form $\frac{1}{30}$ of the total blood contained in the body. By this method the total blood has been calculated to be one-twentieth of the body weight, so that there is a discrepancy between the results obtained by the two methods, though the latter method is probably the more accurate.

CHAPTER VIII.

THE VASCULAR MECHANISM.

SECTION I.

The life of the muscles, of the nervous system, and of every tissue of the body depends upon their receiving an adequate supply of food and oxygen; and one of the most important functions of the blood is to convey oxygen and nutritive material to the tissues and to carry away carbon dioxide and waste products which are formed by the tissues. In order that this function may be carried out, the heart and blood-vessels furnish the mechanism by which a constant circulation of the blood throughout the body is maintained; and by means of the central nervous system the activities of this mechanism can be varied in response to the ever-changing needs, either of the body as a whole, or of its different parts.

The heart acts as a pump, and drives the blood along the arteries, through the capillaries and veins and back to the heart. The actual interchange of nutritive material and waste products between the blood and tissues takes place solely through the walls of the capillaries, and the entire circulatory mechanism is adapted to maintain the conditions most favourable to this interchange.

THE HEART AND BLOOD-VESSELS.

The heart is a hollow muscular organ lying in the thorax between the lungs, and slightly to the left of the middle line of the body. It is conical in shape, the apex being directed downwards, and is divided by a septum into right and left halves, which do not communicate directly with each other. Each half consists of two chambers, an upper thin-walled auricle (atrium) and a lower thick-walled ventricle. Into the right auricle open the superior vena cava, bringing blood from the head and upper limbs, the inferior vena cava, conveying blood from the rest of the body, and the coronary sinus. The right auricle opens into the right ventricle by an orifice guarded by a valve with three triangular

cusps, tricuspid valve, arising from the fibrous junction between the auricle and ventricle and hanging down into the ventricle. The cusps consist of connective and elastic tissue, and are so arranged as to permit the flow of blood from auricle to ventricle, but not in the reverse direction. From each cusp a number of tendinous threads, *chordæ tendineæ*, pass to be attached to projections of the ventricular wall, known as the papillary muscles.

The right ventricle possesses two openings: (1) the auriculo-ventricular just described, and (2) the opening into the pulmonary artery, which conveys blood from the heart to the lungs. The latter opening is provided with a valve having three semilunar cusps composed of strong fibrous and elastic tissue. In the centre of the free border of each cusp is a small fibrous nodule, the corpus Arantii, which serves to strengthen the valve. When the valve is closed, the free borders of the cusps come into contact with each other and are pressed together, thereby preventing the return of blood from the pulmonary artery to the ventricle.

The general arrangement of the left side of the heart is very similar to that of the right. Two pulmonary veins from each lung open into the left auricle. The auriculo-ventricular valve possesses only two cusps; it somewhat resembles a bishop's mitre, and is known as the mitral valve. The cusps, like those of the right auriculo-ventricular valve, are connected by tendinous cords with the papillary muscles and the wall of the left ventricle. Opening out of the left ventricle is the aorta, which is provided with a valve having three semilunar cusps similar in structure to those of the pulmonary artery.

The cavities of the heart are lined by a smooth membrane, the *endocardium*, composed of delicate connective and elastic tissue covered by flattened endothelial cells.

The substance of the heart consists of muscular tissue bound together by connective tissue and supplied with blood from the coronary arteries. It is arranged in sheets composed of fibres, which are built up of short cylindrical segments or cells; each cell has an oval nucleus and shows an indistinct longitudinal and transverse striation. The fibres are branched, the branches of adjacent fibres uniting with one another so that the heart muscle forms a continuous network of cells, known as a *syncytium*.

The wall of the auricles is composed of (*a*) superficial fibres common to both auricles, and (*b*) deep fibres, both looped and annular, proper to each auricle; the annular fibres form muscular rings around the openings of the great veins. The auricles are joined to the ventricles by strong fibrous rings, which encircle the auriculo-ventricular orifices, and by a band of modified muscular tissue, known as the auriculo-ventricular

bundle, or *bundle of His*, the importance of which will be considered later.

The muscular fibres of the ventricles are arranged in a very complex manner. A superficial stratum runs in a spiral direction from the fibrous rings uniting the auricles and ventricles to the apex of the heart; here the fibres form a whorl and then ascend in the interventricular septum and on the inner surfaces of the ventricles to end in the papillary muscles. Between the layers thus formed are deeper fibres, most of which are arranged in an ∽-shaped manner, springing from the papillary muscles of one ventricle and ending in the papillary muscles of the other ventricle; they are united by muscular strands with the layers of the superficial stratum. The muscle is so arranged that, when contraction occurs, the cavities of the ventricles become smaller.

The wall of the left ventricle, which drives the blood through the greater part of the body, is about three times as thick as that of the right ventricle, which drives the blood only through the lungs; the thin-walled auricles merely discharge their contents into the relaxed ventricles. The capacity of the two ventricles is approximately the same, amounting in each case to a maximum of 140 c.c., and is rather larger than that of the auricles

The pericardium is a fibrous sac enclosing the heart, attached below to the diaphragm and lined by flattened cells; where the great vessels pass through it the epithelial layer is reflected and covers the surface of the heart. The smooth inner wall of the sac is moistened by a little lymph (pericardial fluid), and the movements of the heart are carried out with hardly any friction. The pericardium serves to prevent over-distension of the heart, when it is being filled by the inflow of blood from the veins.

The Blood-vessels.—*The arteries*, which convey blood from the heart to the capillaries, are thick-walled tubes made up of muscular and elastic tissue. A medium-sized artery shows three coats—outer, middle, and inner. The outer coat is composed of fibrous tissue. The middle coat consists of smooth muscle fibres arranged circularly, and of yellow elastic fibres. The inner coat consists of flattened endothelial cells united edge to edge by a cement substance, some loose connective tissue, and a thick elastic lamina next the middle coat. The middle coat of the large arteries, such as the aorta, contains a larger proportion of elastic tissue and a correspondingly small amount of muscle, whereas that of the small arteries (arterioles) is purely muscular.

The *capillaries* form a dense network round and among the tissue elements in almost every part of the body, and consist of a single layer

of flattened cells united by cement substance. Their calibre varies slightly, but the average diameter is little wider than that of a red corpuscle.

The *veins* also possess three coats, but their walls are thinner and contain much less muscular and elastic tissue than the arteries, and are strengthened by the presence of a considerable amount of fibrous tissue, especially in the outer coat. Many veins have valves consisting of fibrous tissue covered on each surface by endothelial cells, and so arranged that they allow blood to flow towards the heart, but prevent any flow in the opposite direction.

The arteries remain patent when divided, and a high internal pressure is required to distend their thick muscular and elastic walls, whereas the thin-walled veins collapse when opened, and become distended under a very low pressure.

THE COURSE OF THE CIRCULATION.

The heart beats rhythmically from seventy to seventy-two times a minute. The beat consists of the contraction of the auricles, followed almost immediately by that of the ventricles, and is succeeded by a pause, during which the whole heart is completely relaxed. The contraction of the auricles and ventricles is spoken of as auricular or ventricular *systole*, the period during which the heart is relaxed being called the *diastole*. At each beat the ventricles expel blood into the aorta and pulmonary artery, from which it is distributed by the former to the body as a whole and by the latter to the lungs.

The blood entering the aorta from the left ventricle is conveyed by the arteries arising from it to the capillaries of the various organs of the body, with the exception of the lungs. From these organs it is returned by veins, which unite with each other, eventually forming the venæ cavæ, which open into the right auricle. The blood passes from the right auricle into the right ventricle, from which it is forced into the pulmonary artery; it then flows along the subdivisions of this artery through the pulmonary capillaries into the pulmonary veins (two for each lung), and thence into the left auricle. From the left auricle the blood enters the left ventricle and is again sent out into the aorta (fig. 54).

In the abdomen, the blood passes through a double set of capillaries. The veins which receive blood from the digestive tract and spleen unite to form a single large vein, the portal vein, which on reaching the liver again breaks up into capillaries; these open into the hepatic veins which join the inferior vena cava.

The complete circulation consists therefore of two parts, the one from the right side of the heart through the lungs and back to the left side of the heart, known as the *pulmonary* or *lesser* circulation, the other from the left side of the heart throughout the rest of the body and back to the right auricle, forming the *systemic* or *greater* circulation. As the blood traverses the lungs it takes up oxygen, becoming scarlet in colour (arterial blood). Arterial blood is found in the pulmonary veins, in the left side of the heart, and in the systemic arteries. During its passage through the capillaries in the various tissues the blood loses much of its oxygen, receives carbonic acid, and becomes darker in colour (venous blood). The venous blood is carried along the systemic veins to the right side of the heart and into the pulmonary artery to take up a further supply of oxygen from the lungs.

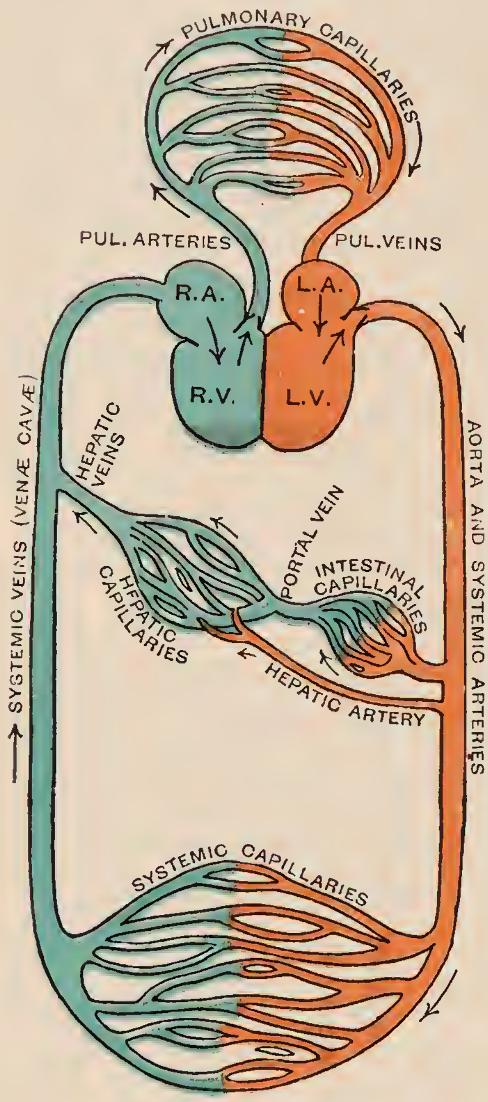


FIG. 54.—Diagram showing the course of the circulation.

THE BLOOD PRESSURE.

When an artery is cut across, the blood spurts out from its central end (the end nearest the heart) with considerable force for some distance; and, evidently, the blood contained in the arteries is exerting a high pressure upon the vessel walls. When a vein is divided, the blood escapes from its peripheral end in a slow steady stream.

The arterial blood pressure can be measured by allowing the blood to flow into a vertical glass tube tied into the central end of an artery. The blood will be seen to attain a height of three or four feet or more, and to show oscillations corresponding with each heart beat. The method is unsatisfactory, partly because the clotting of the blood in the tube soon brings the experiment to an end, partly because, in a small animal, the loss of blood from the body may interfere with the circulatory mechanism. It is customary, therefore, to place in the artery a small cannula, filled with half-saturated sodium sulphate solution to delay clotting, and to connect the cannula with one limb of a U-shaped tube ("manometer") containing mercury, which is so heavy that a column of mercury 100–150 mm. high suffices to counter-

balance the pressure of the blood in the artery, and to prevent the blood escaping into the cannula. A writing point áttached to a float resting on the mercury in the other limb of the manometer can be used to record the pressure on a moving blackened surface (kymograph).

The following method is used (fig. 55). An artery (such as the carotid or femoral) is exposed in an anæsthetised animal, and the flow of blood is shut off by a clip. The artery is ligatured about 2–3 cm. beyond the clip, opened between the clip and the ligature, and a cannula containing a half-saturated solution of sodium sulphate is tied into it. This cannula is connected by thick rubber tubing with a

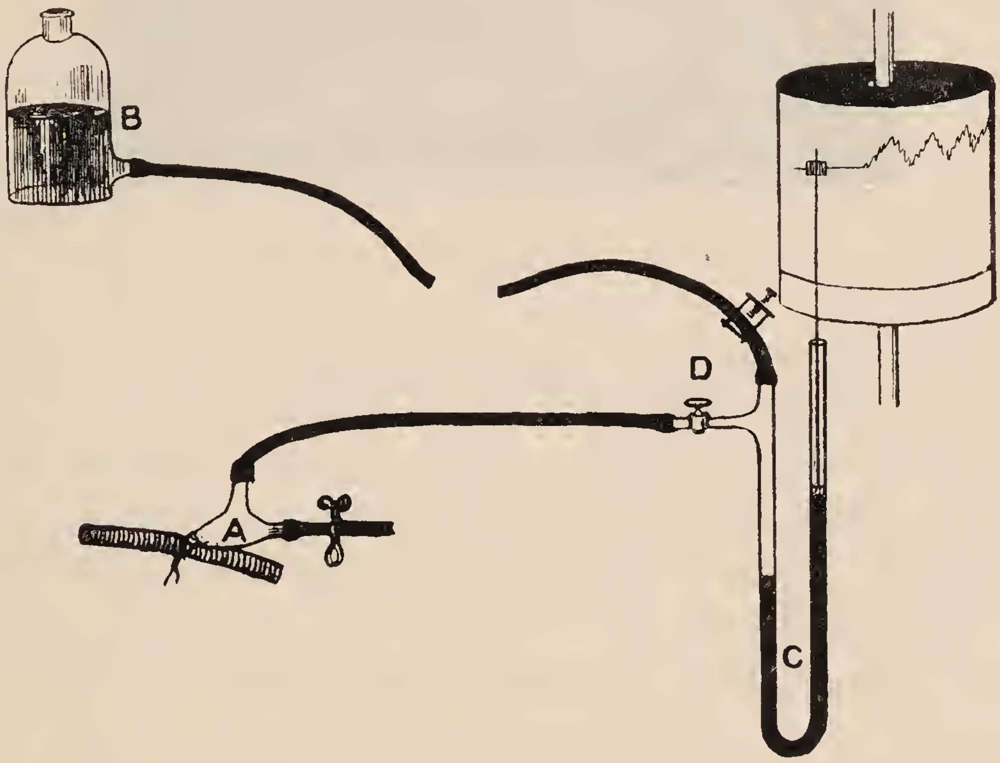


FIG. 55.—Apparatus for taking a blood-pressure tracing.
A, cannula inserted in an artery; B, pressure bottle; C, mercurial manometer.

bottle containing a half-saturated solution of sodium sulphate, and with one limb of the manometer. By raising the bottle the cannula and connecting tubing can be filled with sodium sulphate solution under such pressure that the column of mercury in the limb to which the float is attached rises from 100 to 150 mm. higher than the column in the limb connected with the artery. The connection between the pressure bottle and the manometer is then shut off by a screw-clamp, and the clip is removed from the artery. The column of mercury rises or falls slightly until the pressure counter-balances that of the blood, and the writing lever remains at a constant level, except for slight oscillations with each heart beat and with the respiratory movements (fig. 56). The difference in height of the columns of mercury in the two limbs represents the mean arterial blood pressure.

The pressure in the large veins may be determined in a similar manner, except that, as the pressure is low, the whole manometer is usually filled with sodium sulphate solution. Observations made in this way show that whereas in a systemic artery the mean blood pressure may vary from 100 to 140 mm. Hg and alters slightly with

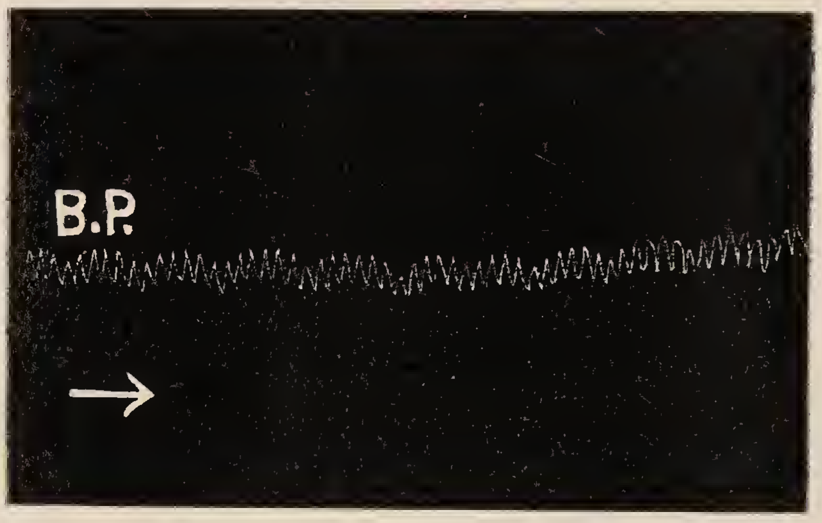


Fig. 56.—Blood-pressure tracing.

each heart beat and respiratory movement, the venous pressure amounts only to a very few mm. Hg and is not affected by the heart beat. It is found that the arterial pressure is highest in the aorta, rather less in the medium-sized arteries, and that there is an abrupt fall of pressure in the arterioles; in the capillaries the pressure is low, and finally there

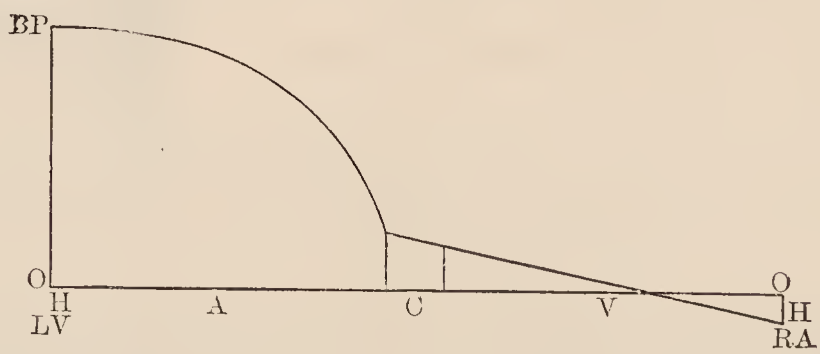


Fig. 57.—Scheme of blood pressure. (Starling's *Principles of Physiology.*)

LV, left ventricle; A, arterioles; C, capillaries; V, veins; RA, right auricle; OO, line of no pressure; BP, blood pressure.

is a steady fall of pressure in the veins, until, in the large veins near the heart, it may actually be negative, that is, less than the atmospheric pressure. These differences of pressure are diagrammatically represented in fig. 57. The pressure in the pulmonary artery varies from 20 to 25 mm. Hg, and on the average is about one-sixth of that in the aorta or its main branches.

We may now consider the factors which are concerned in this distribution of pressure, and in the conversion of the jerky flow

of blood in the arteries into a continuous flow in the capillaries and veins.

They are (1) the beat of the heart, (2) the elasticity of the arteries, and (3) the peripheral resistance.

The action of these factors is a purely mechanical one, and can be reproduced in an artificial scheme such as is shown in fig. 58. A reservoir R containing a coloured fluid is attached to a horizontal rubber tube S T open at its other end, and a number of vertical glass tubes open at the top are connected with this tube. As the fluid flows from the reservoir, it rises in the vertical tubes to a height corresponding with the pressure at that point, and the line A B joining the top of

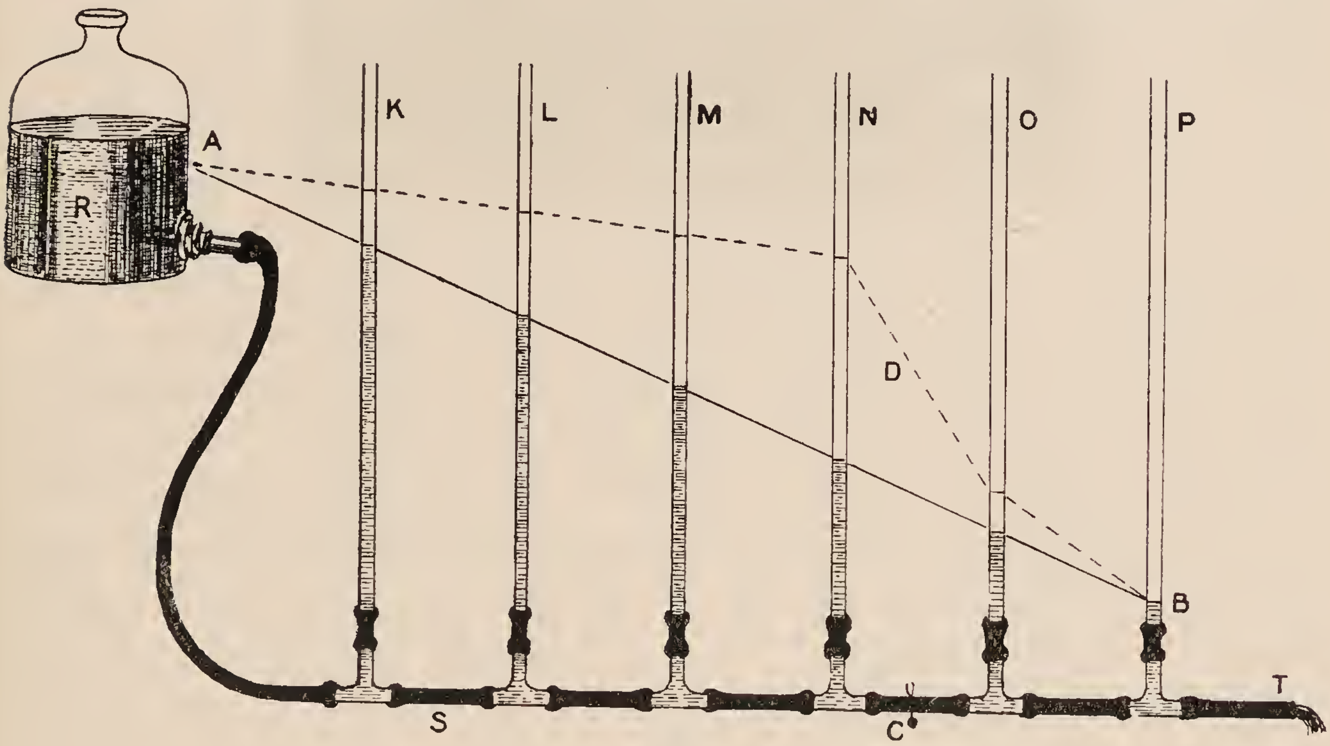


FIG. 58.

the columns of fluid in the tubes shows that there is a uniform fall of pressure along the rubber tube. If a screw clip is placed on the rubber tube at C and gradually tightened, thereby introducing a resistance to the flow of fluid along the tube, the pressure rises on the proximal side and falls on the distal side of the clip, the pressure gradient along the tube being indicated by the dotted line A, D, B.

When the flow of fluid from the reservoir is made intermittent by alternately compressing and releasing the connection between it and the tube at short intervals, the fluid in the vertical tubes K, L, M, and N, between the reservoir and the resistance at C, shows corresponding oscillations in height, whereas in the tubes O and P, beyond C, these oscillations are absent, and fluid flows from the end of the rubber tube in a steady stream.

In the body the reservoir is represented by the heart, which at each beat sends into the aorta a certain quantity of blood (in man about

60 c.c.). The peripheral resistance is due to friction between the flowing blood and the walls of the vessels, the amount of friction varying inversely with the bore of the vessels and directly with the velocity of the blood. The peripheral resistance caused by this friction is very large in the arterioles, which are numerous and of small bore, and in which the blood flows rapidly. In the capillaries the blood flows so slowly that, although their calibre is very minute, the resistance is much less than in the arterioles; and in the large arteries it is comparatively slight.

With each beat of the heart an additional quantity of blood enters the arterial system, and, if there were no peripheral resistance, an equal quantity would *instantly* escape through the arterioles into the capillaries. But the resistance offered by the arterioles is so great that when the blood is forced during systole into the already distended arterial system, there is not an immediate escape of a corresponding amount from the arterioles into the capillaries. Most of the force of the heart is expended in further distending the arteries in order to accommodate this additional blood sent into them, and the pressure within them rises. In the interval between two heart beats the distended arteries shrink by virtue of their elasticity, thereby forcing blood through the arterioles, and the pressure falls slightly. The result is that the flow of blood along the capillaries and veins takes place both during and between the heart beats as a steady stream, whereas blood enters the aorta only during the heart beat, and the flow along the arteries is jerky.

When the amount of blood entering the arterial system during systole is equal to that leaving it, partly during systole and partly during diastole, the mean arterial pressure remains steady. Any increase or decrease in the amount of blood entering the aorta at each beat will tend to raise or lower the arterial pressure. Similarly, dilatation of the arterioles will diminish the resistance to the escape of blood into the capillaries and the arterial pressure will fall, whereas constriction of the arterioles will produce a rise of pressure.

Although the driving force of the heart pump is sufficient to propel the blood round the body and back to the heart, its action is normally assisted (1) by the respiratory movements, which will be considered later (page 283), and (2) by skeletal muscular movements. Every muscular movement tends to squeeze blood along the veins towards the heart, any reflux being prevented by the valves with which these veins are provided.

Mean Systemic Pressure.—When the heart ceases to beat the arterial pressure falls, the venous pressure rises, and finally there is

a uniform pressure throughout the vascular system, the height of which will depend upon the amount of blood present in the vessels. This is called the *mean systemic pressure.* If more blood is added to the vascular system, the mean pressure will rise, and *vice versa.* When the heart starts to beat, it pumps blood into the arteries, which become distended, because at first the outflow from the arterioles is less than the amount of blood forced into the aorta; and the arterial pressure rises. As a result of the transference of blood from the veins to the arteries the venous pressure falls below the mean pressure. It follows, first, that under normal conditions the arterial and venous pressures vary inversely with one another, and, secondly, that the arterial, capillary, and venous pressures will all vary with the total volume of blood in the vascular system, although the venous and capillary pressures are those chiefly influenced.

BLOOD PRESSURE IN MAN.

Arterial Pressure.—The highest blood pressure occurring during the cardiac systole is called the *systolic* pressure; the pressure corresponding with the end of diastole is the *diastolic* pressure, the difference between the two being called the *pulse* pressure. The systolic pressure is measured by means of a Riva-Rocci sphygmomanometer. This consists (fig. 59) of a leather band about four inches wide, inside which is a rubber bag communicating with a mercurial manometer and connected with a small pressure bulb. Attached to the bulb is a screw by which the bag can be put into communication with or shut off from the external air.

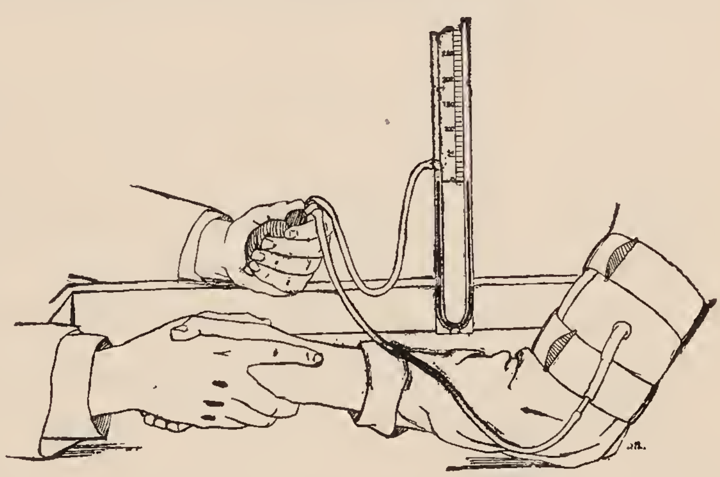


Fig. 59.—Riva-Rocci sphygmomanometer. (From Messrs Hawksley.)

The band is fastened round the upper arm. The observer feels the radial pulse with the fingers of one hand, while with the other he squeezes the bulb and distends the bag with air, until the pressure is just sufficient to obliterate the brachial artery and the radial pulse disappears. When this occurs, the pressure in the mercurial manometer is noted. The screw attached to the bulb is then gently turned, the air slowly escapes, and the pressure falls; when the radial pulse is just perceptible, the pressure in the manometer is again observed. The mean between the two readings is the systolic arterial pressure. This

represents the pressure on the outer wall of the artery which exactly balances the greatest pressure within the artery during systole, and at which the lumen of the artery is just obliterated.

The diastolic pressure can be approximately measured with the same instrument by observing the height of the manometer when the oscillations of the column of mercury with each heart beat are maximal. When this happens, the pressure in the bag is just equal to that in the artery at the end of diastole (diastolic pressure); the artery collapses between the beats and then expands almost fully during systole. Thus the lowest level of the manometer *between* the beats gives a record of the diastolic pressure; and by measuring the diastolic and systolic pressures, the pulse pressure, which is the difference between them, can be determined. The systolic pressure in the healthy adult varies in

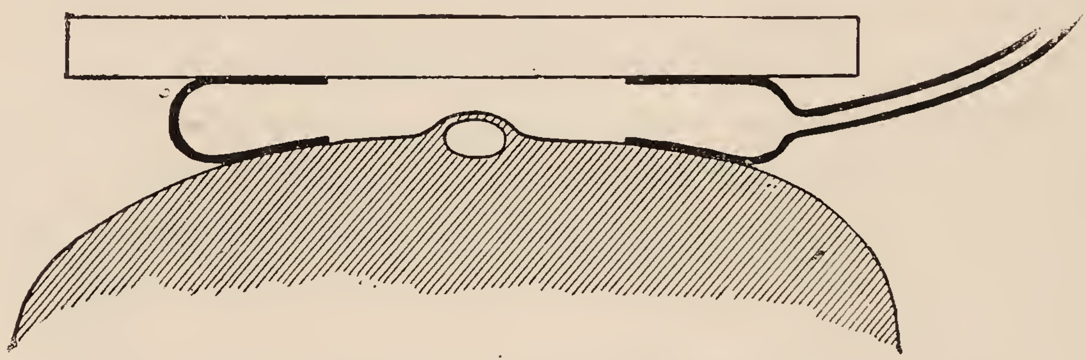


FIG. 60.—(Starling's *Principles of Physiology.*)

the large arteries, such as the brachial, from 100 to 110 mm. Hg; it becomes higher with increasing age, and at fifty, even in health, is about 140 to 150 mm. Hg. It is temporarily raised during muscular or mental work, and falls again during rest.

Venous Pressure.—A flat rubber bag having a hole through the centre of each flat surface (fig. 60) is placed over a peripheral vein and covered by a glass plate, the junctions being made air-tight with glycerol; a tube leads from the bag to a manometer and to a pressure bulb. Air is blown into the bag, the glass plate being firmly held in position; when the pressure reaches a certain height the vein collapses, and the reading of the manometer represents the venous pressure. The same method, a smaller bag being used, may be employed to determine capillary pressure. The average capillary pressure is from 15 to 40 mm. Hg. The venous pressure varies from 8 to 10 mm. Hg in the smaller veins; in the large veins near the heart it is only 1 or 2 mm. Hg, and may be negative.

VELOCITY OF THE BLOOD FLOW.

The average rate of flow in a river depends upon the pressure gradient between its source and the sea; and in the same way the actual velocity of the blood stream is determined by the driving force of the heart pump, that is, upon the amount of blood expelled from it at each beat. If the heart is beating feebly the velocity will be small, whereas if the heart is beating strongly and rapidly, for example during muscular exercise, the velocity may be considerable. These differences are of importance, since the rate at which oxygen is carried from the lungs to the various tissues of the body is largely determined by the rapidity of the circulation.

The *relative* velocity of the blood flow in the arteries, capillaries, and veins is determined solely by the total width of the channels through which the blood is flowing. Since the same quantity of blood has to pass in a given time through each cross-section of the bed of the vascular system, it is obvious that the smaller the cross section the greater must be the velocity of the blood flow. For the same reason the water flows rapidly in a river where the channel is narrow, and slowly where the channel widens out into large pools.

When an artery divides, each branch is smaller than the parent artery, but the total cross section of the two branches is larger than that of the parent artery. The total cross section of the vessels thus increases with each branching, and in the capillaries it has been estimated to be about 800 times as great as that of the aorta. The sectional area of the veins gradually decreases as they unite to form larger vessels, and that of the large veins entering the heart is approximately twice as great as that of the aorta. It has been found that whereas the average velocity of the blood in the large arteries is about 400–500 mm. a second, it varies from $\frac{1}{2}$–1 mm. a second in the capillaries, and is from 200–250 mm. a second in the large veins.

In a small organ, such as the kidney or submaxillary gland, the velocity of the flow of blood is also modified by *local* changes in the arterioles. Dilatation of the arterioles lessens the resistance to the flow of blood through the organ without affecting the general arterial blood pressure, and since the resistance is lessened in that organ as compared with other organs in the body, a short-cut is provided between the arteries and the veins; hence the blood flows through the organ with increased velocity and in increased amount. This result, which furnishes an apparent exception to the general statement made above, is only true when the organ is so small that alterations in the calibre of its arterioles do not appreciably affect the general blood pressure.

Methods of measuring the Velocity of the Blood Flow.—(1) **Ludwig's Stromuhr.**—This consists of two glass vessels A and B connected at the top (fig. 61). On A is a mark *c*, the capacity of the vessel below the mark being exactly known. The vessels are fixed at their lower ends into a metal disc H, placed upon a similar disc N, and capable of being rotated upon the latter through two right angles. The openings *a′* and *b′* in the upper disc fit exactly over those (*a* and *b*) in the lower disc; from these openings in the lower disc arise two tubes F and G. The experiment is carried out as follows. A clip is placed on an artery, which is then divided and connected at one end

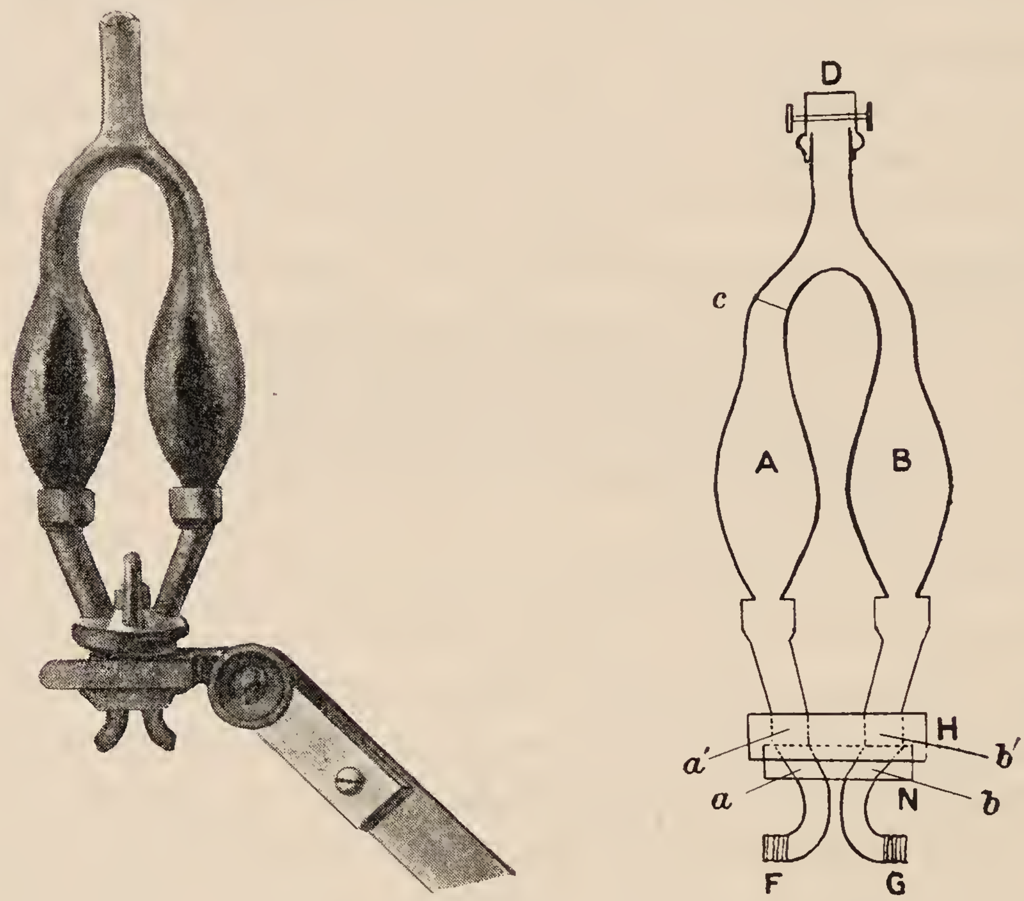


Fig. 61.—1, Ludwig's stromuhr; 2, Diagrammatic representation.

with tube F, at the other with tube G. The tube and the vessel A, which communicate with the proximal end of the artery, are filled with olive oil up to the mark *c*, and the remainder of the apparatus is filled with defibrinated blood. The blood is then allowed to flow through F into A, thus driving the oil over into B and sending the defibrinated blood into the peripheral end of the artery. As soon as the blood leaving the artery reaches the mark *c*, the disc H is turned rapidly through two right angles, and the blood flowing from the artery now drives the oil back into A. When the oil again occupies its original position, the disc is once more rotated through two right angles. This process is repeated as often as necessary, the experiment being carried on for any desired period; clotting of the blood can be prevented by the previous

injection of hirudin into the animal. The diameter of the artery is then measured. From these data the velocity of the blood flow can be calculated by means of the formula

$$\text{Velocity} = \frac{\text{volume (passing through the stromuhr) per second}}{\text{sectional area of blood-vessels.}}$$

If the capacity of the bulb up to the mark *c* is 5 c.c., and it was filled six times in a minute, then the amount of blood passing through the instrument would be 30 c.c. in one minute, or $\frac{1}{2}$ c.c. in one second. Supposing the diameter of the artery to be 2 mm., the sectional area is πr^2, and rate of flow can be calculated as follows :—

$$\text{Velocity} = \frac{0{\cdot}5 \text{ c.c.}}{3{\cdot}1416 \times 1^2} = \frac{500 \text{ c.mm.}}{3{\cdot}1416} = 159 \text{ millimetres per second.}$$

Many other instruments have been devised, of which the most useful is the photohæmatachometer of Cybulski. This consists of two vertical tubes united at the top, and opening below into a horizontal tube, as shown diagrammatically in fig. 62. The proximal end of an artery is attached to the instrument at A, the blood escaping at B into the distal end of the artery. The blood will rise higher in the tube C than in the tube D, the difference in height of the two columns being directly proportional to the velocity of the blood flow in the artery. A graphic record is obtained by allowing a beam of light to throw an image of the menisci of the columns of fluid on to a moving photographic plate. To determine the absolute velocity of the blood, the instrument must be calibrated. It has the advantage of giving not merely the average velocity of the blood flow, but also the variations during ventricular systole and diastole. In one experiment, the velocity varied from 250 mm. per second during systole to 127 mm. in diastole.

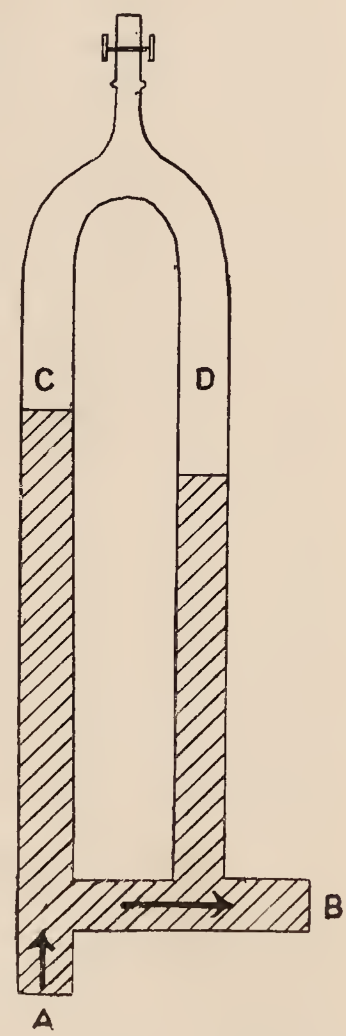


Fig. 62. — Diagram showing the principle of Cybulski's photohæmatachometer.

THE CIRCULATION IN THE CAPILLARIES.

On observing the flow of blood through the small arteries and veins in the mesentery or web of a frog, the red corpuscles are seen to occupy the central part of the vessels (axial zone), and to be moving more rapidly than the peripheral layer of blood, in which are found most of the leucocytes. The formation of the axial zone is due to the

fact that the specific gravity of the red cells is higher than that of the plasma. The lumen of the capillaries is so small that no axial zone is present. The velocity of the blood flow in the capillaries can be directly observed with the aid of an eye-piece micrometer by noting the time taken by a red corpuscle to travel a given distance, and varies from 0·5 to 0·8 mm. per second; and as the average length of a capillary is from 0·4 to 0·8 mm., any one corpuscle traverses the capillary in one second. During this time, the interchange of oxygen and of carbonic acid and of nutritive and waste material between the blood and the tissues takes place through the capillary wall. The capillary pressure is intermediate between that in the arteries and veins, and since the capillaries open directly into the veins the pressure in them is very easily influenced by a rise or fall in venous pressure.

If an irritant, *e.g.* dilute acetic acid, is applied for a moment or two to the surface of the frog's mesentery, the minute arterioles and the capillaries soon become dilated, and the blood flows more rapidly through them. Presently the leucocytes begin to adhere to the capillary walls, and some of them make their way through the interstices between the epithelial cells into the surrounding tissue. At the same time, the capillary wall seems to alter so as to offer more resistance to the flow of blood; and the flow slackens and may cease, although the capillaries and arterioles are still dilated. After a time, the capillaries become filled with a mass of red and white cells, much of the plasma passing through the walls of the capillaries into the lymph. Sometimes the red corpuscles are also forced through the capillary walls, this being called *diapedesis.* This series of events forms part of the process of *inflammation*, which is defined as the response of the tissues to an injury provided the latter does not cause death at once. The injury may be mechanical or may be brought about by chemical substances, including bacterial products.

THE TIME OF THE CIRCULATION.

One of the best methods for determining the circulation time is to inject into one jugular vein a strong solution of methylene blue; the jugular vein on the opposite side is exposed and allowed to rest on a strip of white paper. The interval between the injection and the moment at which the blue colour becomes visible in the opposite vein is observed; it varies from 15 to 20 seconds.

Another method consists in sending a compensated electric current through a section of an artery, *e.g.* the left carotid, and through a galvanometer. A little concentrated salt solution is injected into the opposite

carotid artery. When the salt is injected, it increases the conductivity of the blood, and as soon as the solution reaches the left carotid artery the electric current passes more easily through the artery, the compensation is upset, and the needle of the galvanometer is deflected.

The time thus measured represents, however, merely the time in which a blood corpuscle can complete the shortest possible circuit in the circulatory system; and the average circulation time of the blood as a whole is probably twice or thrice as long as that found by these methods.

SECTION II.

THE PHENOMENA OF THE NORMAL HEART BEAT.

(1) **Changes in Form.**—Observation of the heart, exposed in an anæsthetised animal, shows that the beat begins with contraction of the great veins near the heart, and is followed immediately by the contraction of both auricles (atria), including their appendages. After a brief interval, known as the auriculo-ventricular interval, the ventricles contract synchronously, assuming the form of a short truncated cone. During their contraction the ventricles become shorter from above downwards, and, as the position of the apex remains almost unaltered, the auricles are pulled down towards the apex, and the aorta and pulmonary artery are stretched longitudinally. At the same time, the cross section of the base of the ventricles alters, becoming more nearly circular and smaller. When the contraction of the ventricles ceases, the whole heart remains for a short time at rest (diastole).

(2) **The Sequence of Events within the Heart.**—During diastole the blood is flowing steadily into the right auricle from the great veins, and also from the auricle into the right ventricle, into which the cusps of the tricuspid valve are hanging. When the auricle contracts, it empties most of its contents into the ventricle, any reflux of blood along the great veins being prevented by the simultaneous contraction of the muscular rings round their termination. The ventricle, which is now full of blood, almost immediately contracts, and the cusps of the tricuspid valve, which had already been carried towards each other by eddies set up behind them as the blood flowed from the auricle into the ventricle, are driven firmly into apposition by the pressure of the blood, their thin borders being tightly pressed together so that no blood can escape into the auricle. The contraction of the papillary muscles keeps the chordæ tendineæ taut, thereby preventing any inversion of the valves under the ventricular pressure.

The ventricle is now a closed cavity, and remains so until the

pressure exerted by the contracting muscle upon the contained blood rises higher than that in the pulmonary artery. As soon as this happens, the semilunar valves open, and blood flows into the pulmonary artery from the ventricle, which becomes nearly but not quite empty. When the systole of the ventricle ends and its walls relax, the pressure in its cavity very rapidly falls below that in the pulmonary artery; and the semilunar valves close, effectually preventing any reflux of blood into the ventricle. A fraction of a second later, the pressure in the ventricle becomes less than that in the right auricle, the auriculo-ventricular valve opens, and blood, which during the ventricular systole has been flowing into the auricle from the veins, again begins to enter the ventricle. The valves open or close with the slightest difference of pressure on either side. During ventricular systole the efficiency

FIG. 63.—Diagram to show the position of the mitral valves in diastole (1) and in ventricular systole (2).

A, auricle; V, ventricle.

of the tricuspid valve is assisted by the diminution of the cross section of the base of the heart. A similar series of changes takes place simultaneously in the left side of the heart (fig. 63).

The series of events just described constitutes a *cardiac cycle*, and occupies on the average a period of 0·8 second. The cycle may be regarded as beginning with the auricular systole, which lasts 0·1 second, and is followed by the ventricular systole, which lasts approximately 0·3 second; during the remainder of the cycle, 0·4 second, the heart is completely relaxed. When the heart is beating infrequently the duration of the cycle is lengthened, and when the heart is beating frequently it is shortened. These differences are due almost entirely to variations in the time occupied by the diastolic pause, the time taken up by the systole of the auricles and ventricles being remarkably constant.

(3) **Cardiac Impulse.**—If the hand be placed on the chest in man,

an impulse will be felt corresponding with each heart beat. It is most distinctly felt, and is often also visible, in the fifth intercostal space, about an inch below and slightly internal to the nipple. The impulse is due to a combination of two causes. In the first place, the left ventricle, which lies in contact with the chest wall, and is soft and flabby during diastole, becomes hard and tense with the onset of systole. The sudden hardening of the ventricle gives a push to the soft tissues of the chest wall with which it is in contact, thereby giving rise to the cardiac impulse. In the second place, the curved aortic arch tends to straighten out when the tension within it is raised by the entrance of blood from the heart. The same phenomenon may

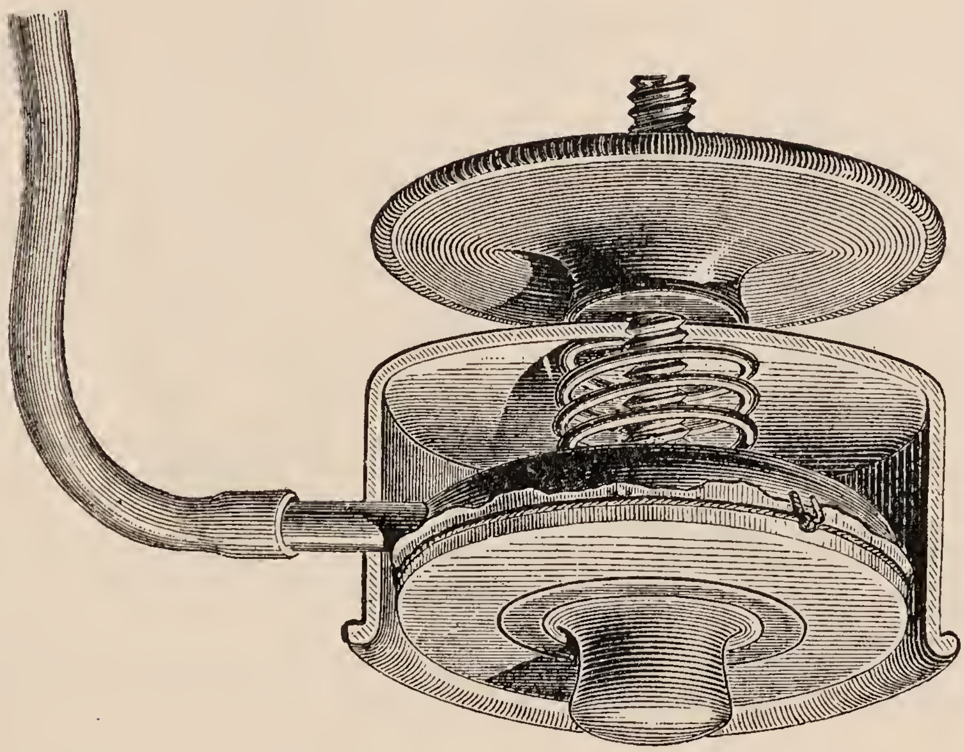


FIG. 64.—A cardiograph. (From Messrs Baird & Tatlock.)

be readily observed in any curved elastic tube filled with fluid, into which more fluid is suddenly forced. The posterior end of the aortic arch rests against the vertebral column and ribs, and cannot alter its position; the anterior end, to which the heart is attached, is, therefore, pushed more firmly against the chest wall.

Although this impulse is often spoken of as the apex beat, the area of the left ventricle which is in contact with the chest wall is some distance above the actual apex of the heart.

A graphic record of the cardiac impulse (cardiogram) is obtained by means of an instrument known as a *cardiograph*. One form of cardiograph (fig. 64) consists of a tambour, the membrane of which is provided with an ivory button which can be placed on the chest at the position of the cardiac impulse: the tambour is connected with a second tambour provided with a recording lever. Another method of

obtaining a cardiogram is to use a polygraph (p. 208), and to place over the region of the cardiac impulse the small metal receiver which is generally used for recording the venous pulse. The general form of the tracings is shown in fig. 75, but it varies considerably with the pressure used and with the spot at which the instrument is applied to the chest.

(4) **The Heart Sounds.**—If a stethoscope is applied to the front of the chest, two sounds are heard with each beat of the heart. They are often compared with the sounds lūbb dŭp, the first being long and low-pitched, the second short and sharp. The time relation between

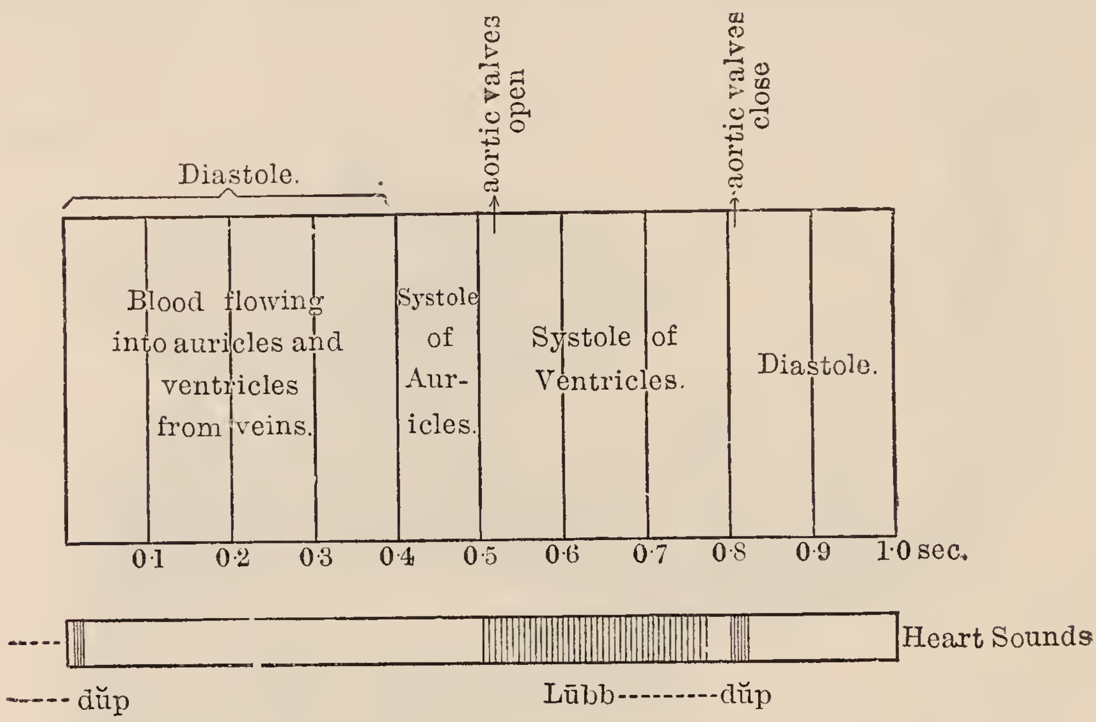


Fig. 65.—Diagram of events constituting a cardiac cycle. (Starling's *Principles of Physiology.*)

the heart sounds and the other events occurring during the cardiac cycle (fig. 65) has been determined in the following manner. A stethoscope is connected with an apparatus similar to the receiver of a telephone; the vibrations of air in the stethoscope, set up by the heart sounds, throw the membrane of the receiver into vibrations and so alter the contact between the silver and carbon which form part of the receiver, and through which a current is passing. The current also passes through an electro-magnet, which pulls on a disc connected with the membrane of a recording tambour. Each vibration of the membrane of the receiver alters the strength of the current passing through the electro-magnet and the pull which it exerts on the iron disc and then on the membrane of the tambour. In this way the vibrations of the receiver caused by the heart sounds can be recorded. If such a record is obtained simultaneously with a cardiogram, it is found that the first sound occupies nearly the whole

of the systole, and that the second sound lasts for a brief space at the commencement of diastole.

The first sound is due to two causes, namely, (1) the vibrations set up by the closure of the tricuspid and mitral valves, and (2) the contraction of the muscular wall of the ventricles. When the tricuspid or mitral valves become diseased so that they fail to close, the first sound is largely replaced by a "blowing" noise, known as a murmur or *bruit*. That the contraction of the heart muscle contributes to the first sound is shown by the fact that, during the contraction of the bloodless, excised heart, a faint sound can be heard with the stethoscope. The duration of the first sound almost to the end of systole furnishes additional evidence that its origin is partly muscular. The relative importance of the valvular and muscular factors is still a matter of discussion. The part of the first sound due to the muscular contraction is not peculiar to the heart, since a similar sound is produced by any note of low pitch, and may be heard on listening to a contracting voluntary muscle.

The second sound is due entirely to vibrations set up in the semilunar valves by their sudden closure at the end of systole, and is replaced by a murmur if these valves are diseased, or if, in an animal, they are hooked back and prevented from closing. The first sound is most distinctly heard near the apex beat; the closure of the aortic valves is best heard in the second right intercostal space close to the sternum, and the closure of the pulmonary semilunar valves in the second left intercostal space.

(5) **Endocardiac Pressure.**—The pressure within the auricles and ventricles rises during systole and falls in diastole, and the variations in pressure are closely bound up with the other events taking place during the cardiac cycle. The changes in pressure occur so rapidly that a slowly moving fluid, such as mercury, fails to record them accurately, although a maximum and minimum mercury manometer may be employed to ascertain the highest and lowest pressure occurring during a cardiac cycle.

In the early observations of Chauveau and Marey a cardiac sound, consisting of a long rigid tube having at its lower end a bulb of very thin rubber supported on a metal framework, was passed along the jugular vein into the right ventricle, or along the carotid artery into the left ventricle, of a horse. The upper end of the sound was attached to a Marey's tambour (fig. 66), which consists of a shallow metal cup having a small lateral opening and covered by a thin rubber membrane on which rests a light lever. The whole apparatus contains air, and any rise of pressure in the ventricle compresses the rubber bulb, thereby

raising the membrane of the manometer and the lever: the movements of the lever are recorded graphically on a kymograph.

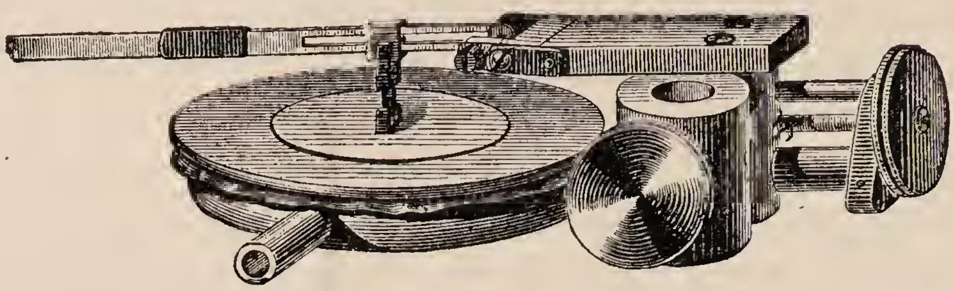


Fig. 66.—Marey's tambour. The writing point of the lever is not shown. (From Messrs Baird & Tatlock.)

The method is unsatisfactory, because, in the first place, it is only applicable to large animals, and, secondly, because, owing to the compressibility of the air contained in the apparatus and to the oscillations of the membrane of the manometer, waves are produced upon the tracing which sometimes render it inaccurate.

These drawbacks are considerably diminished in Hürthle's method, the essential features of which are (1) the use of a very small manometer with a thick rubber membrane (fig. 67), (2) the substitution for the sound of a tube opening directly into the ventricle, and (3) the filling of the whole apparatus, including the tambour, with fluid (half-saturated sodium sulphate solution).

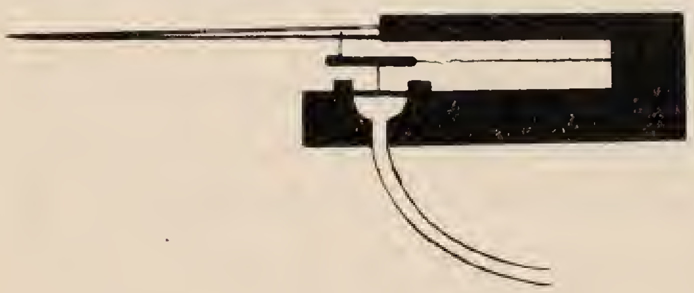


Fig. 67.—Hürthle's manometer.

A still better manometer has recently been devised by Piper, in which instrumental errors are almost completely excluded (fig. 68). It consists of a metal cannula A, 6 cm. in length, containing a trocar B, by the aid of which the cannula can be thrust through the wall of the auricle or ventricle into the cavity of the heart. It is filled with saline solution containing hirudin, and even the smallest air bubble must be excluded. The cannula expands at C to form a small chamber, one wall of which is covered by a thick stretched rubber membrane D; to the outer surface of this membrane a tiny plane mirror E is attached.

When the cannula has been pushed into the heart and tied in position, the trocar is withdrawn and the tap F is closed so as to prevent the escape of blood; the cannula is then fixed with a clamp. As the endocardiac pressure varies, the membrane bulges or shrinks slightly and the position of the mirror alters; these movements are recorded and greatly magnified by throwing on to the mirror a beam of light, which is reflected on to a kymograph covered with photographic paper and excluded from other sources of light.

The advantages of this method are, first, that the movements of the membrane are directly proportional to the variations in pressure, and by the elimination of a lever are recorded without inertia, and, secondly, that when the membrane is thrown into vibrations these are so rapid (250 per second) that they cannot possibly be mistaken for oscillations produced by changes in the endocardiac pressure, and are so rapidly damped that they practically do not occur when the pressure is recorded. A similar cannula may be passed into an artery so as to record the changes in arterial pressure.

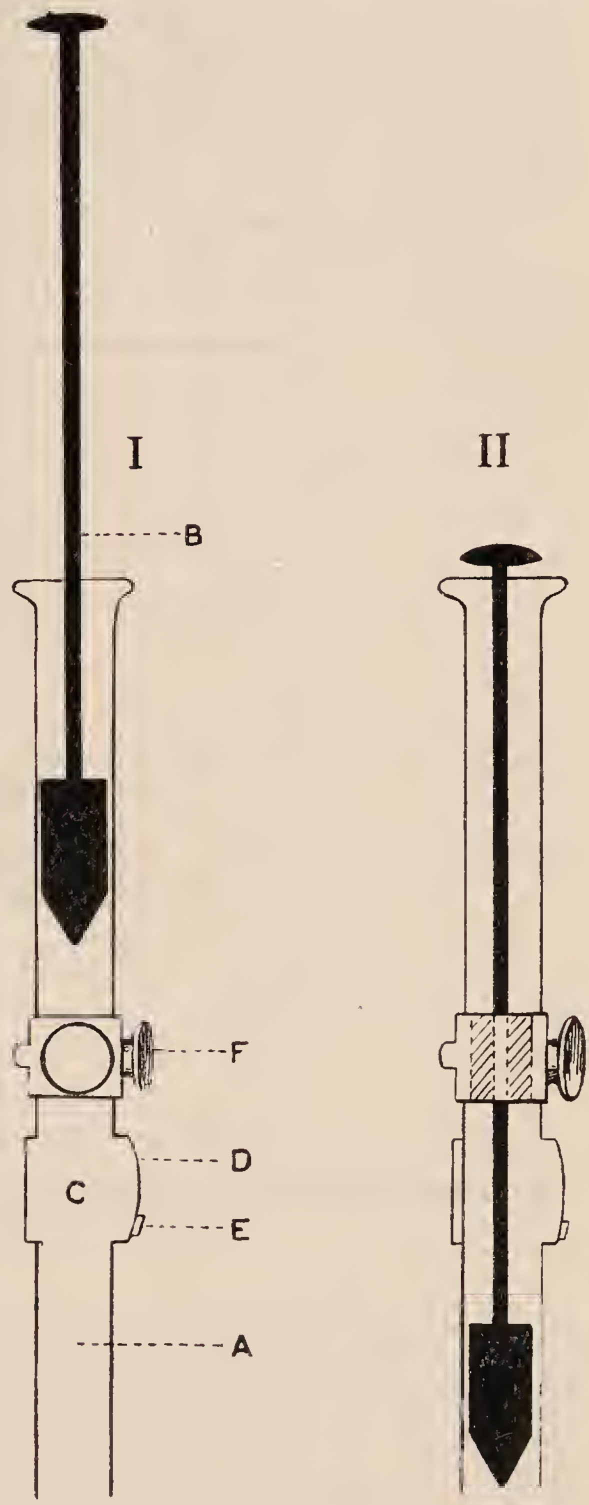


FIG. 68.—Piper's manometer. Explanation in the text.

Fig. 69 represents a record, obtained by this method, of the pressure changes in the left auricle and ventricle and in the aorta during a cardiac cycle. The middle curve representing intra-ventricular pressure shows at 1 a slight elevation (not always present) due to the auricular systole. This is followed almost immediately by the systole of the ventricle, which begins at 2 and occupies the period between 2 and 3; it usually lasts from 0·25 to 0·3 second. At first the curve rises very steeply; the auriculo-ventricular valves close at the point *a*, and from *a* to *b* the ventricle is a closed cavity. At *b* the intra-ventricular pressure becomes higher than that in the aorta, the semilunar valves open, and blood flows from the ventricle into the aorta during the whole period from *b* to 3, when the ventricle ceases to contract. The notch in the ascending part of the tracing immediately after the point *b* is due to the fact that, when the semilunar valves open, the escape of blood from the ventricle is momentarily impeded by the inertia of the column of blood in the aorta.

The portion of the tracing from *b* to 3 lasts about 0·18 second, and is generally known as the systolic plateau; it resembles a plateau, however, only when the arterial pressure is low, and its usual shape would be more accurately described as the systolic arch.

When the systole ends at 3, the intra-ventricular pressure rapidly falls; a short distance down the descending part of the tracing, namely, at the point *c*, the pressure in the ventricle falls below that in the aorta, and the semilunar valves close; their closure does not alter the form of the intra-ventricular record, though it causes a series of small oscillations in the aortic pressure. At the point 4, the pressure in the ventricle falls below that in the auricle, the mitral valve opens, and blood flows into the relaxed ventricle.

Auricular Pressure.—A record of the pressure changes in the auricle presents three main waves (fig. 69). The first corresponds with

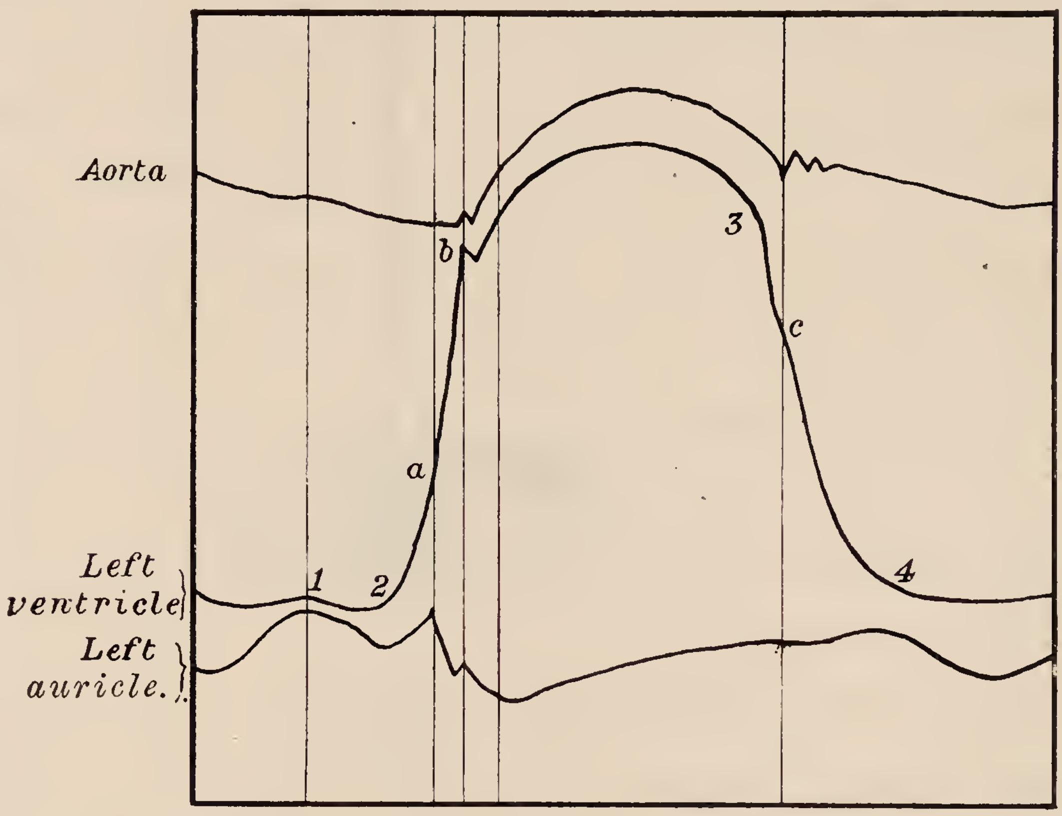


Fig. 69.—Simultaneous record of the changes of pressure in the aorta, left ventricle and left auricle. (From Piper.)

the auricular systole, the second with the sudden closure of the auriculo-ventricular valves, and the third, which occurs toward the end of ventricular systole, is due to the filling of the auricle with blood while the auriculo-ventricular valves are still shut.

The maximum pressure in the left ventricle of the dog is usually from 140 to 160 mm. Hg, and in the right ventricle from 25 to 30 mm. Hg.

THE OUTPUT AND WORK OF THE HEART.

When the ventricles contract, they force blood into the aorta and pulmonary artery against the blood pressure in these vessels. In so doing the heart performs work, the amount of which may be determined by the formula $W = Q \times R$, where W is the work done, Q is the

amount of blood expelled from the ventricles (output of the heart) at each beat, and R is the resistance against which the heart is working; R is approximately represented by the average arterial pressure.

The output of the heart may be indirectly measured by enclosing the heart in an apparatus (cardiometer) which fits closely round the base of the ventricles, and is connected with some form of tambour and recording lever. When the ventricles contract and expel blood into the arteries, their volume diminishes, and, since the apparatus is air-tight, there is a corresponding fall of the recording lever.

One of the simplest forms of cardiometer is a glass vessel resembling a large thistle funnel, the mouth of which is covered by a rubber membrane with a hole in its centre. When the heart is placed in the cardiometer, the border of the membrane fits closely in the auriculo-ventricular groove, forming an air-tight junction. The cardiometer is

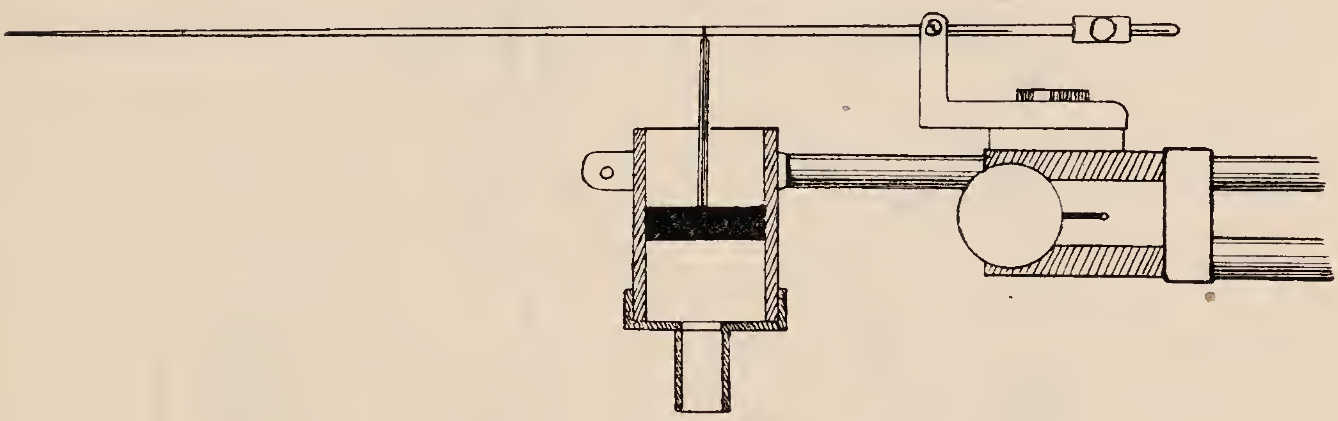


Fig. 70.—Piston recorder. (Diagrammatic.)

attached to a piston recorder, which is more sensitive than an ordinary tambour, and consists of a vulcanite piston fitting closely in a cylinder, the latter having an opening at its lower end by which it can be connected with the cardiometer: a light counterweighted lever is attached to the piston (fig. 70). The piston moves very easily, and its excursions are proportional to the changes in volume of the heart. In order to obtain a quantitative measurement of the output of the heart the instrument is calibrated.

Another and direct method of determining the output of the heart is the heart-lung preparation (fig. 71), devised by Knowlton and Starling. The common carotid artery, the descending aorta, and the inferior vena cava are ligatured, and cannulæ containing a solution of hirudin in normal saline solution are placed in the innominate artery and the superior vena cava. The blood leaving the left ventricle through the innominate artery passes through a thin rubber tube A; this can be compressed to any desired extent by means of a pump C and pressure bottle D, the resistance thus offered to the flow of blood through the tube replacing the

resistance of the arterioles. The cannula in the artery is also attached to a mercurial manometer F, which records the arterial pressure. The small cylinder E contains air, which forms an air cushion and to some extent replaces the elasticity of the arterial wall. After traversing the tube A, the blood enters a cylinder B in which it is warmed and from which it passes into the superior vena cava, and then through the lungs to the left side of the heart. The circulation is thus confined to the heart and lungs, artificial respiration being maintained by a pump.

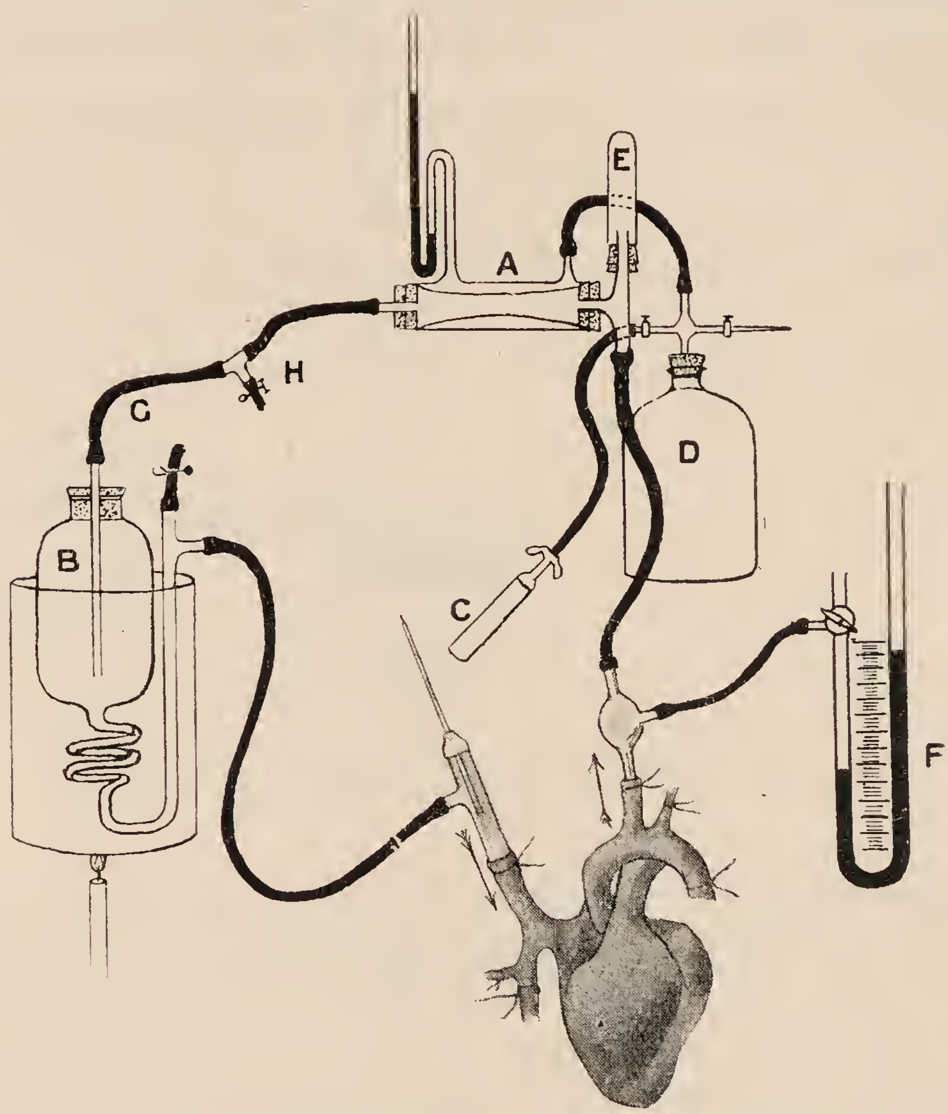


Fig. 71.—Arrangement of apparatus in the heart-lung preparation. (Knowlton and Starling.) Description in the text.

The output of the left ventricle in a given time, *e.g.* five seconds, can be measured by clamping the tube G, opening the clip on H, and allowing the blood to flow into a graduated vessel instead of into the cylinder; and if the rate of the heart is observed, its output at each beat can be calculated.

In man, the output of the heart has been indirectly determined in the following manner. The individual takes a deep breath of air containing a certain amount of nitrous oxide, which is very soluble in blood. After a few seconds he expires deeply, a sample of the expired alveolar air being collected in the manner described on p. 251.

He then holds his breath for twenty to thirty seconds and again expires deeply, a second sample of alveolar air being collected. The total amount of air in the lungs at the beginning and end of the (experimental) period between the two expirations is determined by indirect means. During this period nitrous oxide is taken up in solution by the blood as it passes through the lungs, its solubility being such that 1 c.c. of blood, if exposed to an atmosphere of pure nitrous oxide, will take up 0·43 c.c. of the gas.

From these data the amount of blood passing through the lungs in a minute can be calculated. To take an example, the volume of air in the lungs at the beginning of the experimental period is 3·25 litres, and contains, as shown by the analysis of the first sample, 12 per cent. nitrous oxide; the total quantity of nitrous oxide in the air of the lungs is $\frac{3250 \text{ c.c.} \times 12}{100} = 390$ c.c. At the end of the period the total volume of air in the lungs is 3·0 litres; the percentage of nitrous oxide in the second sample of expired air is 10 per cent.; and the lungs contain 300 c.c. nitrous oxide. Thus 90 c.c. nitrous oxide have been taken up by the blood; and the mean percentage of nitrous oxide in the air in the lungs is $\frac{12 \text{ per cent.} + 10 \text{ per cent.}}{2} = 11$ per cent.

With this percentage of nitrous oxide in the air of the lungs, each 1 c.c. of blood passing through them will take up $\frac{0{\cdot}43 \times 11}{100} = 0{\cdot}047$ c.c. nitrous oxide; and in order to take up 90 c.c., 1·9 litres of blood must have passed through the lungs during the experimental period. If the experimental period lasted twenty-seven seconds, the flow of blood through the lungs per minute is 4·2 litres. This figure represents the output from the right ventricle during that period, and if the pulse rate is 70 per minute, the output per beat will be $\frac{4200 \text{ c.c.}}{70} =$ 60 c.c. per beat. This figure may be taken as representing the average output of each ventricle in man, since in health the output of the two ventricles is the same.

The mean arterial pressure in man is about 100 to 110 mm. Hg. From these data the work done by the heart at each beat can be calculated. Thus $Q \times R = 60$ grm. $\times$ 0·100 metre $\times$ 13·6 (specific gravity of mercury being 13·6 times that of blood) = 81·6 grm. metres. This figure represents the work done by the left ventricle. If the pressure in the pulmonary artery be taken as 20 mm. Hg, the work done by the right ventricle will be 60 grm. $\times$ 0·02 metre $\times$ 13·6 = approximately 16·4 grm. metres.

The total work of the heart, therefore, is in this instance about 98 grm. metres per beat.

The heart expels blood not only against the peripheral resistance, but with a certain velocity. The work (W) done in imparting this velocity to the blood is measured by the formula $W = \frac{MV^2}{2g}$, where $M =$ mass of blood expelled, $V =$ its velocity, $g =$ the force of gravity; it amounts to approximately 1 per cent. of the total work of the heart and is practically negligible.

We may now consider the conditions which determine the output and the work of the heart.

The Output of the Heart.—It has already been pointed out that, when a skeletal muscle contracts, the contractile stress developed in it is proportional to the initial length of the muscle fibre, *i.e.* its length just before it begins to contract, and that if the muscle is stretched by means of a weight it contracts more forcibly. The heart muscle behaves in exactly the same way, the only difference being that, in the case of the heart, the initial length of its muscle fibres depends upon the stretching of the fibres produced by the contained blood. Hence the greater the amount of blood present in the heart at the beginning of systole, the greater the initial length of the fibres, and the greater the force with which they contract. The result is that within wide limits the amount of blood expelled from the ventricles at each beat is determined solely by the amount entering the heart during diastole. This amount is increased (1) by deeper respiratory movements, whereby more blood is sent into the heart with each inspiration; (2) by muscular movement, which drives blood along the veins towards the heart; and (3) by any increase in the total volume of the circulating blood, such as is produced by the injection of saline solution into a vein. During exercise the more forcible respiration and the active muscular movement lead to a much larger output of blood than during rest. There is a certain optimum filling of the heart and initial length of the muscle fibres at which the mechanical efficiency of the muscle during contraction is at its best; excessive filling of the heart may dilate it to such an extent during diastole as to diminish its efficiency, and its output falls.

The output of the heart is not affected, except for a moment or two, by alterations in the arterial blood pressure unless these are extreme. The first effect of a rise of blood pressure is that for a few beats the ventricle empties itself less completely, its volume during diastole being thus increased. This distension of the ventricle during diastole increases the length of the fibres, causing them to contract

more strongly during systole, and the output of the heart again becomes as large as it was at the lower arterial pressure (fig. 72).

The capacity of the ventricle to maintain its normal output in spite of a greatly raised arterial pressure is spoken of as its "power of compensation," and is of the utmost importance. In its relation to the body as a whole the output of the heart is one of the fundamental facts of the circulation, since it determines the supply of oxygen to the tissues; and if the output were diminished whenever the blood pressure rose, for example during exercise, the high blood pressure

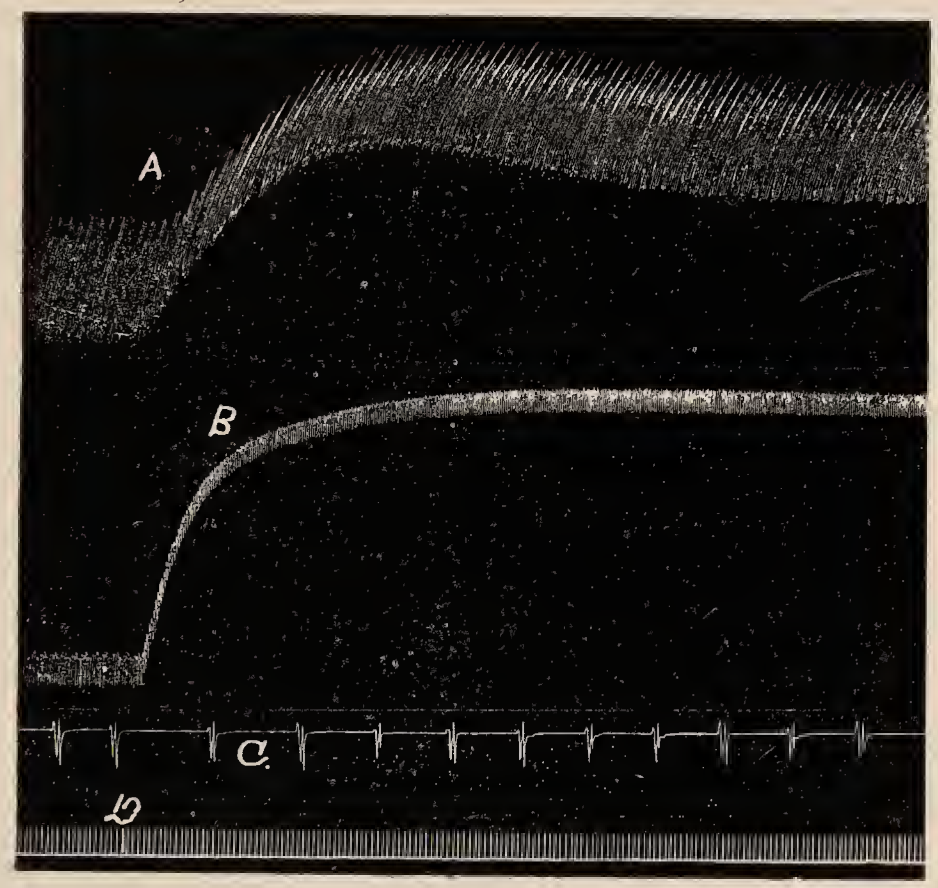


Fig. 72.—Output of heart. (Knowlton & Starling.)
A, volume of ventricle: B, arterial pressure; C, output of left ventricle; D, time in seconds.

would necessarily involve a smaller and possibly inadequate supply of oxygen to the tissues.

If the arterial pressure becomes very high, the dilatation of the left ventricle during diastole is so great as to diminish its efficiency when it contracts, the output of the heart falls, and the left auricle empties itself less completely into the already distended ventricle. In consequence, the left auricle contains more blood, the pressure within it rises, and blood passes less readily from the lungs into the auricle and accumulates in the pulmonary veins and capillaries. This accumulation of blood in the lungs is spoken of as their "reservoir" action, and helps to prevent excessive dilatation of the left side of the heart.

The compensatory power of the heart enables it to adapt itself to transient variations in arterial blood pressure. When the work of the heart is permanently increased by a continuously high blood pressure, the heart wall hypertrophies, just as skeletal muscles enlarge as the result of exercise. The effort of prolonged increase in the work done by the heart is seen in the hypertrophy observed in athletes (athlete's heart).

When the heart beats rapidly the diastolic pause is shortened, less blood enters it between the beats, and its output per beat is diminished. Hence its output in a given time (*e.g.* a minute) is not necessarily greater when the heart is beating rapidly than when it is beating slowly. The increased rate of the heart, however, which usually accompanies increased diastolic filling, is of advantage, since by preventing over-distension during diastole it enables the heart to contract under the most favourable conditions as regards its mechanical efficiency.

Work of the Heart.—Since the work done by the heart is measured by its output multiplied by the arterial pressure (Q × R), it will be altered either by a rise or fall of arterial pressure, or by variations in the output of the heart, or by these two factors varying simultaneously. Whenever the arterial blood pressure rises the heart does more work, since the output remains unchanged. Again, increased filling of the heart brought about by any of the causes already mentioned, by increasing its output, will add to its work; and the larger output from the heart tends in itself to raise the arterial blood pressure, and thus to increase still further the work done. In muscular exercise there is both a rise of arterial blood pressure and a greater diastolic filling of the heart.

In man, during exercise, the output of the heart per beat may be 90 to 100 c.c., and since the heart is beating much more rapidly, its output per minute may be two or three times as great as during rest, and its work is enormously increased. These facts indicate how important it is that persons, whose hearts have become less efficient owing to disease, should be kept at rest.

SECTION III.

THE PULSE.

If the arterial system consisted of a series of rigid tubes, the blood forced into it from the heart would, in accordance with the laws of hydrostatics, cause an instantaneous rise of pressure throughout the whole system, and an equal quantity of blood would at once escape from the distal end of the system. Owing to the fact that the arteries are distensible, only a fraction of the blood entering the arterial system at

each beat is forced through the arterioles during the beat, and much of the force of the heart is expended in further expanding the already distended arterial system to accommodate the extra blood sent into it. The expansion of the arteries starts at the root of the aorta, and proceeds as a wave along the whole arterial system, gradually dying away before the capillaries are reached. This wave of expansion constitutes the pulse. It travels at a rate of 6 to 8 metres a second, and is independent of the movement of the main mass of blood along the arteries, the velocity of which rarely exceeds half a metre a second.

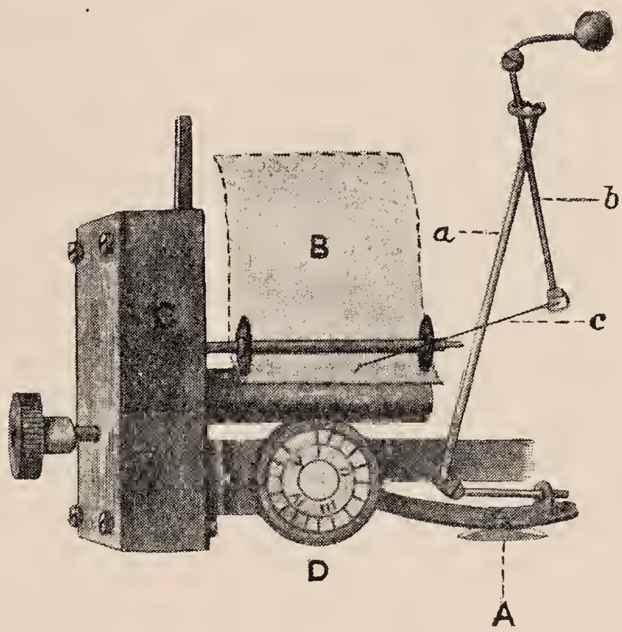


FIG. 73. — Dudgeon's sphygmograph, slightly diagrammatic. Explanation of figures in text.

The pulse can be felt, and often seen, in the superficial arteries of the body, *e.g.* the radial artery; in order to study it more exactly a graphic record may be obtained by means of an instrument known as a *sphygmograph*, of which many forms exist.

Dudgeon's sphygmograph, which is illustrated diagrammatically in fig. 73, may be attached by a band round the wrist in such a way that the small metal plate A rests on the skin over the radial artery. The movements of the arterial wall are magnified by the series of levers, *a*, *b*, *c*, and are recorded by the free end of the lever *c*, which writes on a moving strip B of blackened (smoked) paper. The paper is moved by means of a small clockwork arrangement; and by means of the dial D the pressure of the plate A on the artery can be adjusted.

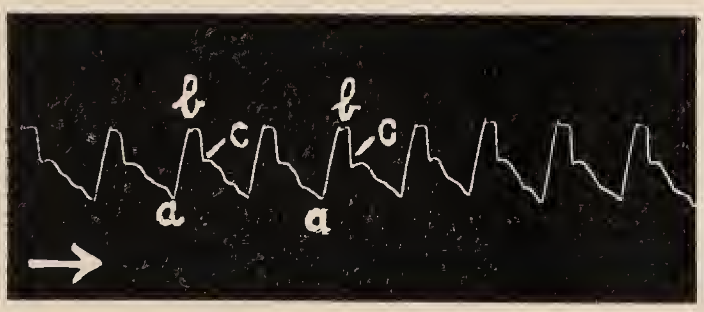


FIG. 74.—Pulse tracing from the radial artery.

A typical pulse tracing thus obtained is seen in fig. 74. It shows a sharp rise from *a* to *b*, succeeded as a rule by a steady fall, interrupted at *c* by a small notch which is immediately followed by a slight wave. The rise *a* to *b* constitutes the primary or percussion wave; the wave following *c* is the dicrotic wave, the notch just preceding it being the dicrotic notch. Other small waves, some preceding the dicrotic wave (pre-dicrotic), and others following it (post-dicrotic), sometimes occur; they

are due to slight oscillations of the stretched arterial walls, which are magnified and distorted by vibrations set up in the sphygmograph. The portion of the wave from *b* to *c* is normally descending, and the pulse is called *katacrotic;* when the primary wave continues to rise almost until the dicrotic notch is reached, the pulse is said to be *anacrotic.*

The primary wave is caused by the sudden expansion of the artery during the cardiac systole, the form of the wave depending upon the peripheral resistance. After the first abrupt rise of arterial pressure the blood usually escapes through the peripheral resistance more rapidly than it enters the arterial system from the heart, and the pulse is katacrotic. When the peripheral resistance is very high, *e.g.* in old age or in Bright's disease, blood continues to enter the aorta during systole more rapidly than it passes through the arterioles; the arterial pressure continues to rise almost to the end of systole, and the pulse is anacrotic.

In the aorta the primary wave begins coincidently with the opening of the semilunar valves and the escape of blood into the aorta, as may be seen in fig. 75, which gives a simultaneous record of the endocardiac pressure and of a pulse tracing. Since this wave of expansion travels from the aorta to the peripheral vessels, the percussion wave begins in the smaller vessels an appreciable time later than in the aorta. This can be readily observed by taking simultaneously two pulse tracings, one from the carotid artery and one from the radial artery at the wrist. By measuring the interval with the aid of a time marker and noting the difference in distance from the heart of the points at which the tracings are made, the velocity of the pulse wave can be measured. Thus, if the interval is one-tenth of a second and the difference in distance is 0·6 metre, the velocity is 6 metres per second. The length of the wave is from 5 to 6 metres.

Fig. 75 also shows that the dicrotic wave occurs immediately after the closure of the semilunar valves, and as no corresponding wave is present in the endocardiac pressure tracing, the dicrotic wave must have its origin in the arterial system. It has been thought that as the primary wave passed along the arteries it was reflected, as a secondary wave, from the obstructions set up wherever the arteries branched, and particularly from the arterioles where the branchings are very numerous. This small reflected wave, starting at the periphery, was believed to travel back towards the heart as the dicrotic wave. Such a wave is actually produced in an artificial scheme of the circulation where the pulse wave beats upon a peripheral resistance.

If this view were correct, the distance between the primary and dicrotic waves would naturally be less in the peripheral arteries near the seat of origin of the reflected wave than in the aorta. But the interval

between the summits of the primary and secondary waves is of the same length in pulse tracings taken from the same individual at the same time, whether the artery examined be near or far from the heart; for example, it is the same in the carotid and the dorsalis pedis arteries.

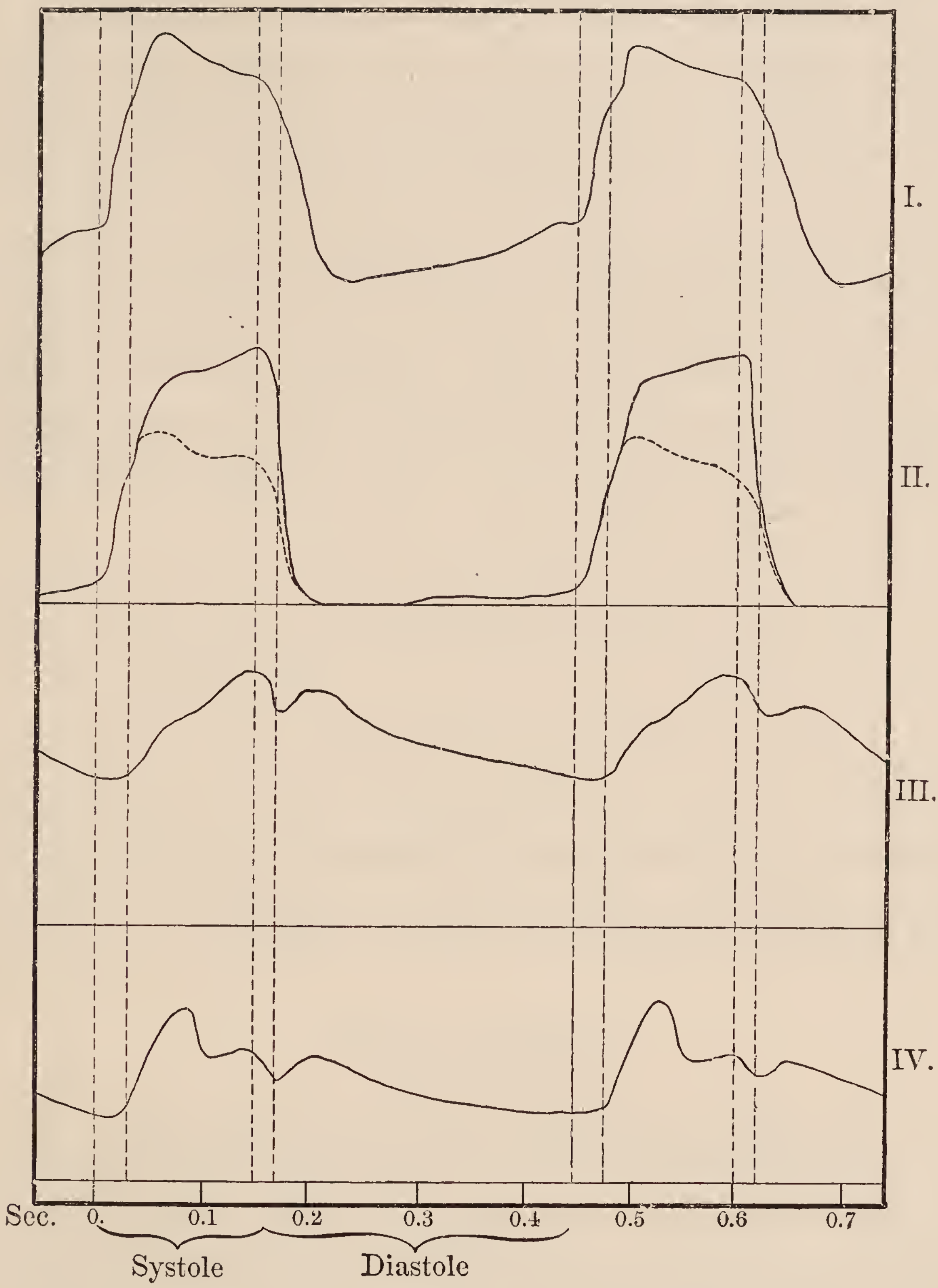


FIG. 75.—Diagram (after Hürthle) showing simultaneous cardiographic, endocardiac, and aortic curves. (Starling's *Principles of Physiology.*)

I., cardiogram; II., endocardiac pressure; III., aortic pressure; IV., aortic pressure, corresponding with dotted endocardiac curve in II.

Hence the dicrotic wave must arise at the same point as the primary wave, and since the primary wave starts at the root of the aorta, the dicrotic wave must start there also.

It is brought about in the following manner. When the left ventricle ceases to contract, the column of blood travelling along the

aorta continues to move in virtue of its momentum, thereby producing a slight fall of pressure at the root of the aorta; and the wall of the artery shrinks a little. This slight fall of pressure immediately causes a reflux of blood against the semilunar valves, closing them, and from the closed valves the blood rebounds, thereby producing a small secondary expansion of the aorta; this expansion travels along the arterial system and forms the dicrotic wave. The height of both the primary and dicrotic waves is largely determined, first, by the elasticity of the arteries, and, secondly, by the degree of distension of the arteries between successive heart beats. If they have become rigid (from old age or disease), their capacity for expansion will obviously be diminished; and if they are already greatly distended by a high mean arterial blood pressure, their capacity for further distension will also be decreased. The conditions most favourable to the appearance of a marked dicrotic pulse, therefore, are (1) a strongly beating heart, (2) a moderate blood pressure, (3) highly elastic arteries. These conditions are often very fully realised in young adults during fever.

The rise of pressure caused by the entrance of blood into the arterial system with each heart beat produces its maximum effect where it first enters it, namely, at the root of the aorta, and the wave of expansion is largest at this point. Some of this rise of pressure is used up in expanding the first section of the aorta, and the force tending to distend the next segment will be slightly less; this process continues from segment to segment along the arterial system, the wave gradually becoming smaller and smaller, until in the capillaries it has entirely disappeared and no trace of any pulse is visible.

VENOUS PULSE.

A venous pulse is normally present in the great veins near the heart, and direct observation of the jugular vein shows two visible pulse waves for each heart beat. In order to obtain a record of the venous pulse and to interpret it, a simultaneous tracing of the venous pulse and of the radial pulse is obtained by means of the *polygraph*. This consists of a clockwork arrangement, whereby a continuous record of the venous and radial pulses can be obtained on a moving sheet of paper. It is provided also with a time-marker, which records on the paper. A small metal cup with an opening at its base is pressed on to the skin over the jugular vein just above the clavicle, and is connected with a tambour attached to a lever which writes on the recording surface. A sphygmograph, attached to the wrist, is also connected by rubber tubing with a similar tambour and lever, and the two levers are

arranged to write one above the other. Fig. 76 represents a tracing of the venous pulse taken by this method.

The venous pulse shows three waves; the first rise, *a*, corresponds with the auricular systole, the second, *c*, is simultaneous with the beginning of the ventricular systole, and the third more rounded wave, *v*, is due to the gradual filling of the auricle towards the end of ventricular systole. The waves correspond with the changes of pressure in the auricle, being transmitted along the column of blood in the vein.

The venous pulse is confined to the large veins, and as the arterial pulse is extinguished in the arterioles, there is normally no pulsation in the medium-sized and smaller veins. The arterial pulse wave may, however, extend into the smaller veins under certain conditions. When the chorda tympani nerve is stimulated, for example, the arterioles of the submaxillary gland are dilated, and not only is the amount of blood

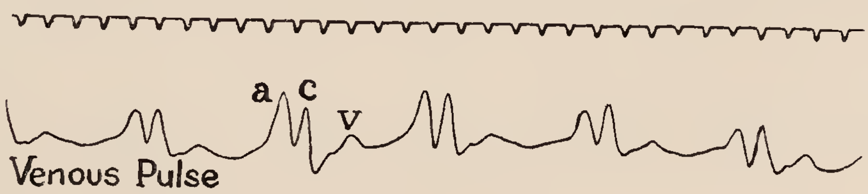


FIG. 76.—Time-marker records $\frac{1}{5}$ secs.

flowing through the gland increased, but the pulse wave extends into the veins coming from the gland. The transmission of the pulse into the veins is due, in this and similar cases, to the diminution of the resistance in the arterioles, which is a consequence of their dilatation.

SECTION IV.

THE CAUSATION OF THE HEART BEAT.

We have now to consider how the beat of the heart originates, and the conditions upon which its normal rhythm depends and by which that rhythm can be modified. For this purpose the slowly beating and relatively simple heart of the frog has proved to be of great value.

Anatomy of the Frog's Heart.—The frog's heart consists of a sinus venosus, two auricles (atria), a ventricle, and a bulbus arteriosus. The blood from the venæ cavæ enters the sinus, passes into the right auricle, and thence into the ventricle. The blood coming from the lungs enters the left auricle and passes into the ventricle. The ventricle opens into the bulbus arteriosus, from which the aortic arches arise and distribute the blood to the entire body, including the lungs. The cardiac muscle

consists of small spindle-shaped fibres showing cross striation, which is very indistinct, particularly in the sinus venosus.

Two nerves, the right and left vago-sympathetic nerve trunks, enter the heart at the sinus, and become connected with a small mass of nerve cells which lies close to the sino-auricular junction and is known as Remak's ganglion. Nerve fibres from this ganglion pass along the septum between the auricles to enter two similar ganglia (Bidder's ganglia), lying close to the auriculo-ventricular junction. Scattered nerve cells are also found in the interauricular septum and in the upper part of the ventricle, but are absent from its apical half. The fibres issuing from all these groups of nerve cells terminate in relation with the muscular fibres of the heart.

THE BEAT OF THE FROG'S HEART.

If the brain of a frog is destroyed and the heart exposed, it can be seen that each beat consists of a regular sequence of events, namely, (1) contraction of the sinus, followed by that of (2) the auricles, (3) the ventricle, and finally (4) the bulbus arteriosus. When the whole heart is carefully excised from the body and placed in a watch glass containing salt solution (0·65 per cent. NaCl), it continues to beat in a normal fashion for some time. On separating the sinus from the rest of the heart, by cutting through the sino-auricular junction, the sinus continues to beat as vigorously and at the same rate as before, whereas the auricles and ventricle cease to beat.

After a short time the auricles and ventricle again begin to beat, but at a slower rate than the sinus. If the ventricle is cut away from the auricles, the latter continue to beat, while the ventricle after one or two beats usually comes to a standstill. After an interval of half an hour or more the ventricle may again begin to beat, and it will do so more readily if it is stimulated by an occasional pin-prick. The rate of the ventricular beat is slower than that of the auricles. The apical half of the ventricle, if isolated, will never again start to beat of its own accord. This experiment makes it clear, first, that the rhythmic beat of the heart can be carried on quite independently of the central nervous system, and secondly, that this power of rhythmic contraction is most fully developed in the sinus.

It was formerly supposed that the beat originated in the nerve cells of the heart, from which a constant stimulus was sent out to the heart muscle, and that the muscular fibres responded to this stimulus by a series of rhythmic contractions. This is the *neurogenic* theory of the cause of the heart beat. The view now generally held, however, is that

the cardiac muscle possesses an inherent power of rhythmic contraction, which is most marked in the sinus and least so in the ventricle, and that this rhythmic power can continue absolutely independently of either the central nervous system or the nerve cells in the heart, although, as will be seen later, it can be influenced by impulses passing along the nerves to the heart. This view is known as the *myogenic* theory of the heart beat. The myogenic theory has been accepted for the following reasons.

(1) In the first place, it was shown by Gaskell that a strip of the ventricle of the tortoise, if kept stretched and moist, can be made to beat rhythmically, and will then continue to beat without any external stimulus, although subsequent histological examination of the strip shows that it contains no nerve cells. In the same way the apical half of the frog's ventricle, which is free from nerve cells, although it will not beat spontaneously, can be made to contract rhythmically if it is fed with fluid through a cannula at a pressure sufficient to put tension on the muscle fibres.

(2) Secondly, it is possible in the frog's heart to remove almost completely the ganglia of Bidder and Remak without disturbing the cardiac rhythm in any way.

(3) Thirdly, if, in a normally beating heart, successive single stimuli are applied to the ventricle more frequently than the rate at which the heart is beating, the rhythm of the heart can be reversed, so that the beat starts in the ventricle and passes to the auricle, and then to the sinus. Such a reversal of rhythm is quite incompatible with the neurogenic theory of the heart beat, since it contradicts the general law (law of forward direction) that nervous impulses can pass through a synapse only in one direction.

It may be concluded, therefore, (1) that the rhythmic contraction of the heart is myogenic in origin, and (2) that, although all parts of the heart possess some rhythmic power, the beat normally always starts in the sinus, in which this power is most fully developed. The sinus sets the pace of the heart, and the ventricle responds to the stimuli reaching it, doing its work under the control of the sinus.

The Propagation of the Beat.—In the frog the muscular tissue of the whole heart is continuous, but the power of the tissue uniting the sinus and the auricles and the auricles and ventricle to conduct impulses is less than that of the rest of the heart. The impulses starting from the sinus are slightly delayed, therefore, in their passage to the auricles, and again in their passage from auricles to ventricle, so that there is a distinct pause between the contractions of the sinus and auricles, and auricles and ventricle respectively.

THE PROPERTIES OF CARDIAC MUSCLE.

If a fine thread is tied round the apex of the frog's heart and attached to a light lever supported by a spring, a graphic record of the heart movements can be obtained; this shows a small fall corresponding with each auricular contraction, and a larger fall corresponding with each ventricular systole (fig. 77). A thread, tightly tied at the junction between the sinus and the auricles, will now bring the auricles and ventricles to a standstill for a variable time, since the ligature prevents the passage of the normal rhythmic stimuli from the sinus to the rest of the heart; this is known as the Stannius ligature. The quiescent ventricle may then be used to study the properties of cardiac muscle as compared with those of skeletal muscle.

The contraction of cardiac muscle shows the following characters:—

(1) When the ventricle is stimulated with single shocks of gradually increasing strength, it is found that with a certain strength of current the heart gives a beat. If a stronger current is used, the resulting beats are not increased in extent or force. The observation that if the heart beats at all in response to a stimulus its contraction is maximal, whatever the strength of the stimulus, is known as the "all or none law." It is due to the fact that the heart muscle is a syncytium, and that a stimulus applied to any point will, if it is effective, spread over the whole muscular tissue of the heart. The heart gives the best beat of which it is capable at any moment, but the force with which it beats will be influenced by various considerations, including the nutrition of the fibres. The "all or none law" simply means that the heart beat is maximal for the conditions under which it is placed at any moment, and not that it remains constant through life. In this respect cardiac muscle behaves like the individual fibres of a skeletal muscle which also obey the "all or none law" (p. 22).

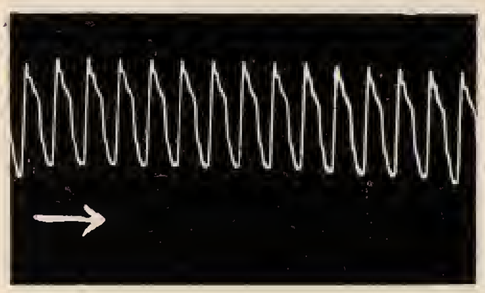


Fig. 77.—Tracing of the normal heart beat in the frog.

(2) If the resting heart is stimulated by successive induction shocks at an interval of 5 to 10 seconds, the height of the second contraction is rather greater than that of the first. At the third or fourth contraction a maximum is reached, and succeeding contractions are all of the same height. This phenomenon is sometimes called the "staircase effect," and is due to the beneficial influence of the first two or three stimuli on the contractile power of the heart muscle. The same effect may be observed in skeletal muscle in similar circumstances.

(3) When the heart is made to beat by a single induction shock,

and a second shock is sent into the heart during the systole evoked by the first stimulus, the second stimulus produces no visible effect on the heart, which is said to be "refractory." This "refractory period" extends from the instant when the first stimulus is applied until the end of the systolic phase. Owing to the length of the refractory period of cardiac muscle as compared with that of skeletal muscle, it is impossible to tetanise the heart, since only those stimuli which fall during the diastolic period are effective.

The refractory period also accounts for the effect observed in the normally beating heart when a single shock is sent into the ventricle at the beginning of diastole. In this case the ventricle responds with an extra beat, and the stimulus coming down from the sinus to produce the next ventricular systole falls within the refractory period of this

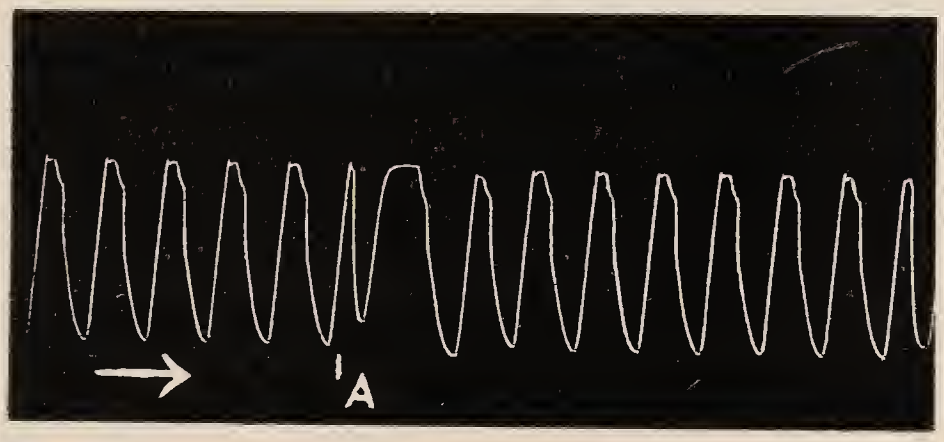


Fig. 78.—Normally beating frog's heart tracing. A single induction shock, applied to the ventricle at A, caused an extra systole, followed by a compensatory pause. Downstroke = systole.

extra beat and is ineffective. There is consequently a long pause, which is known as the "compensatory pause," between the extra beat and the next beat originating from the sinus (fig. 78).

(4) The force of the contraction is greatly influenced, as in the case of skeletal muscle, by the tension to which the fibres are exposed, that is, by the length of its fibres. If the heart is isolated and perfused with saline solution (0·65 per cent. NaCl), the force of the ventricular contraction will vary with the pressure under which the fluid is allowed to enter the heart. The higher the pressure, the greater will be the amount of saline solution entering the ventricle during diastole; and the pressure of the fluid will put tension on, and thus increase the length of, the muscle fibres. The heart muscle has the power of responding to the increased tension by contracting more strongly, with the result that it empties itself as completely as it did when the pressure of the perfusing fluid was low. Increase of internal tension is thus a stimulus to contraction, and it is for this reason that the apical half of the frog's heart contracts rhythmically when it is

filled with fluid under pressure. The heart of the snail is so susceptible to this stimulus that it will not beat at all unless its fibres are under tension.

THE MAMMALIAN HEART.

In the mammalian heart the sinus, although present in early embryonic life, does not exist as a separate structure after birth, but is represented by a mass of specialised tissue, lying close to the entrance of the superior vena cava into the heart, and extending a little way along the sulcus terminalis of the right auricle. This tissue is known as the sino-auricular node.

It has already been mentioned that connecting the auricles and ventricles is a band of tissue known as the *bundle of His.* This bundle starts near the opening of the coronary sinus into the right auricle, its point of origin being called the auriculo-ventricular node. It passes along the top of the interventricular septum for a short distance, and then divides into two branches, one of which runs down the right and the other down the left wall of the septum immediately under the endocardium. In some animals, *e.g.* the calf, it can be readily dissected out in this part of its course as a thin band, paler than the rest of the ventricular muscle. It soon breaks up into a number of very fine branches which pass partly to the papillary muscles, and are partly distributed over the rest of the wall of the heart. The extent of this branching is well seen in fig. 79. Microscopically, the fibres making up the terminal branches of the bundle are larger and paler than ordinary cardiac muscle fibres, and only the peripheral part of the fibre shows cross striation, the centre being protoplasmic in character; the fibres are called Purkinje's fibres.

The Rhythm of the Mammalian Heart.—Although the heart is provided with many nerve cells and receives in addition a nerve supply from the central nervous system, its rhythm in the mammal, as in the frog, is in all probability of myogenic origin and depends solely upon the inherent rhythmic power of the muscle itself. It has been shown, for example, that provided they are adequately supplied with oxygenated blood, strips of mammalian ventricle will continue to beat for some hours although they contain no nerve cells. Evidence to the same effect is furnished by the heart of the embryo chick, which begins to beat some days before any nerves are present in it.

The impulse normally starts in the sino-auricular node, and, travelling over the walls of the auricles, reaches the auriculo-ventricular node. From this node, the impulse passes along the bundle of His to the ventricles. The importance of the bundle of His is manifested by the

effects which follow either disease of the bundle in man, or division of the bundle in animals. In man the continuity of the bundle may be partially or completely destroyed by disease, the result being known as partial or complete "heart block." In partial heart block one out of every two or three auricular beats is conducted to the ventricle, the latter beating at half or a third the rate of the auricles (2 : 1 or 3 : 1 rhythm). In complete heart block the rhythm of the auricles is unaffected,

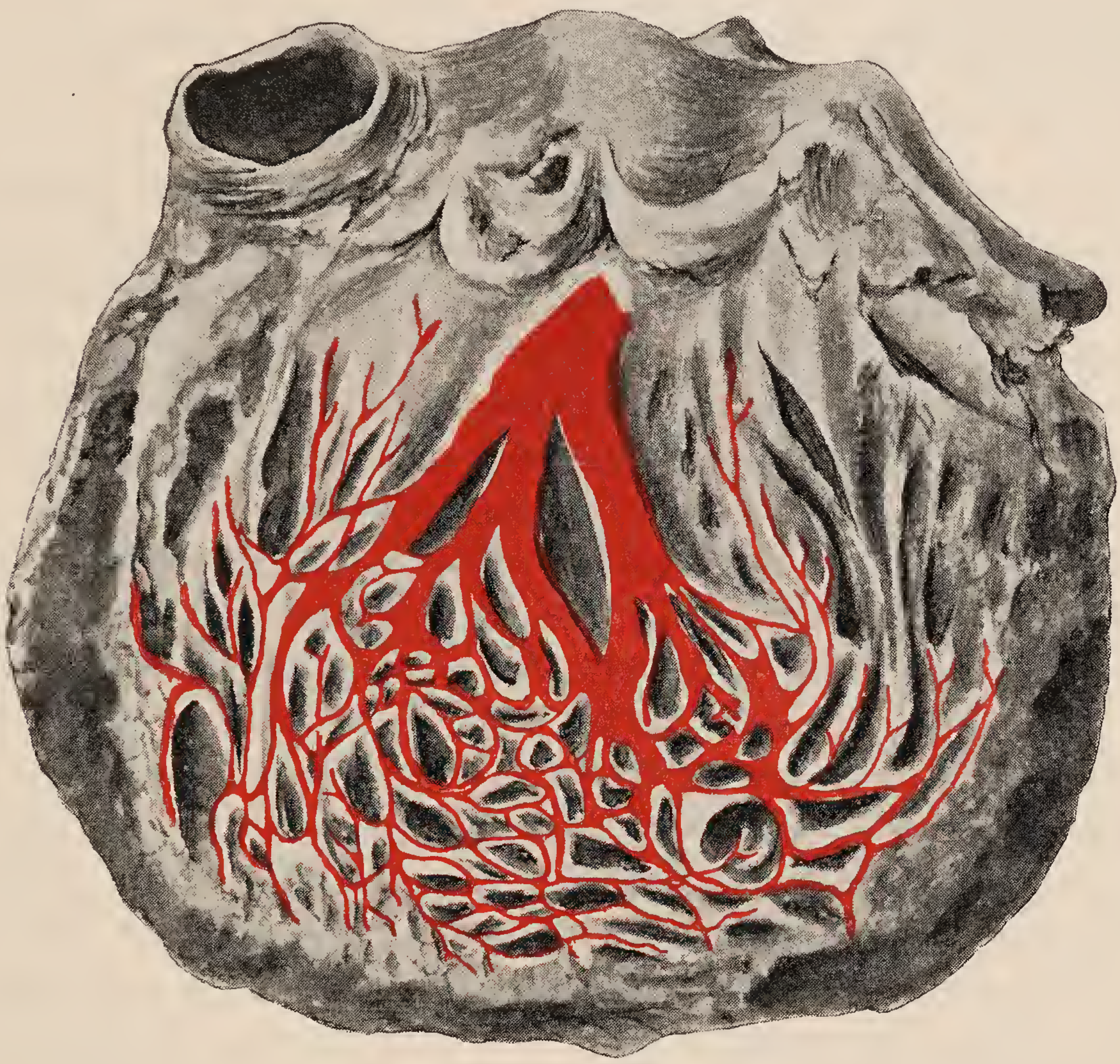


FIG. 79.—Diagram to show the distribution of the bundle of His (in red) in the wall of the left ventricle. (After Tawara.)

whereas the ventricles beat at a rate varying from 20 to 40 per minute; the patient usually exhibits characteristic symptoms (Stokes-Adams disease), and a simultaneous record of the venous and radial pulse, taken with the polygraph, shows that the rhythm of the ventricles is quite independent of that of the auricles.

When the bundle is divided in an animal, the rhythm of the auricles remains unaltered, whereas the ventricles immediately begin to beat at a slow rate having no relation to that of the auricles. Partial heart block is sometimes seen in asphyxial conditions, even when the bundle is intact. Partial or complete heart block can also be induced in the frog's heart by compressing the tissue uniting the auricles and

ventricle so as to lessen or abolish its conductivity. The mammalian ventricle differs, however, from that of the frog in possessing a more pronounced rhythmic power, and when functionally isolated from the auricles, it immediately begins to beat with its own rhythm.

It is evident that the bundle of His is essential for the propagation of the wave of contraction from the auricles to the ventricles.

The Electrical Changes in the Heart.—The time relations of, and the course taken by, the wave of contraction, as it travels from the sino-auricular node over the heart, can be easily demonstrated, not only in the lower animals, but even in man, by studying the electrical changes which take place at the same time. These changes may be recorded by connecting two parts of the heart, for instance the auricles and ventricles, with some form of galvanometer. For this purpose, the string galvanometer (p. 24) is now most generally used.

The resting heart is isoelectric, that is to say, the auricles and the ventricles are at the same potential, and the thread of the galvanometer is at rest. When the auricles contract, a difference of potential is set up between them and the ventricles, and a current passes in the heart from auricle to ventricle, and through the galvanometer from ventricle to auricle. During systole of the ventricles and diastole of the auricles, the current passes in the opposite direction. Cardiac muscle thus resembles skeletal muscle in that its contraction is preceded by an electrical change, the contracting part being galvanometrically negative (but electro-positive) to the resting part. The difference in character of the galvanometric tracings of the electrical changes in the heart and in skeletal muscle is due, partly to the prolonged contraction of cardiac muscle fibres, partly to the complex arrangement of these fibres in the heart wall.

In order to obtain a record of the electrical changes in the human heart, one end of the thread of the galvanometer is connected with a vessel containing salt and water into which the right arm of the subject is placed. The left leg is placed in a similar vessel connected with the other end of the thread. The right arm is regarded as conducting the electrical changes at the base of the heart, while the changes occurring at the apex are conveyed down the left leg to the apparatus. The apparatus is so arranged that in these circumstances an upward movement of the shadow of the thread on the photographic record means that the base of the heart is negative to the apex, and is therefore contracting, while the apex is at rest.

Fig. 80 represents an electro-cardiogram obtained with this instrument, and shows three upstrokes for each cardiac cycle. The first

wave, P, corresponds with the systole of the auricles, which, when they contract, become galvanometrically negative to the resting apex. The second wave, R, occurs at the beginning of the ventricular systole, and is due to the systole commencing at the base of the ventricle, which becomes negative to the apex. As the wave of contraction travels to the apex, the thread returns to its resting position and remains steady for a short time, during which the whole ventricle is in contraction. The final rise at T is due to the systole lasting longer at the base than at the apex, particularly round the root of the aorta and pulmonary artery. The records obtained in the lower animals show the same general form; in the frog and tortoise the prolonged contraction of the ventricle is accompanied by a long period between P and T during which the heart is isoelectric.

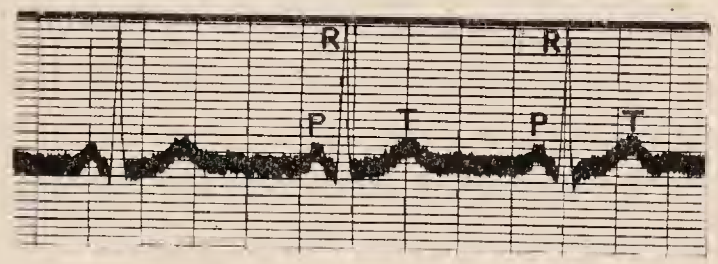


Fig. 80.—Electro-cardiogram from human heart. (Hume.) Explanation of letters in text.

The Nutrition of the Heart Muscle.—The nutrition of the heart muscle is dependent on the amount and composition of the nutrient fluid supplied to it, that is, in normal conditions, of the blood. The influence of alterations in the composition of the nutrient fluid are very easily studied in the isolated frog's heart, the muscular wall of which is nourished entirely by interchanges between the muscular fibres and the blood flowing through the heart. For this purpose a cannula, such as that shown in fig. 81, is tied into an auricle, and the heart is excised. The cannula is attached to a bottle containing a suitable perfusion fluid, which enters the heart at a pressure of 1 to 2 cm. of water. The fluid expelled through the bulbus arteriosus from the ventricle flows over the surface of the heart, keeping it moist. The apex of the ventricle is connected by a thread with a recording lever.

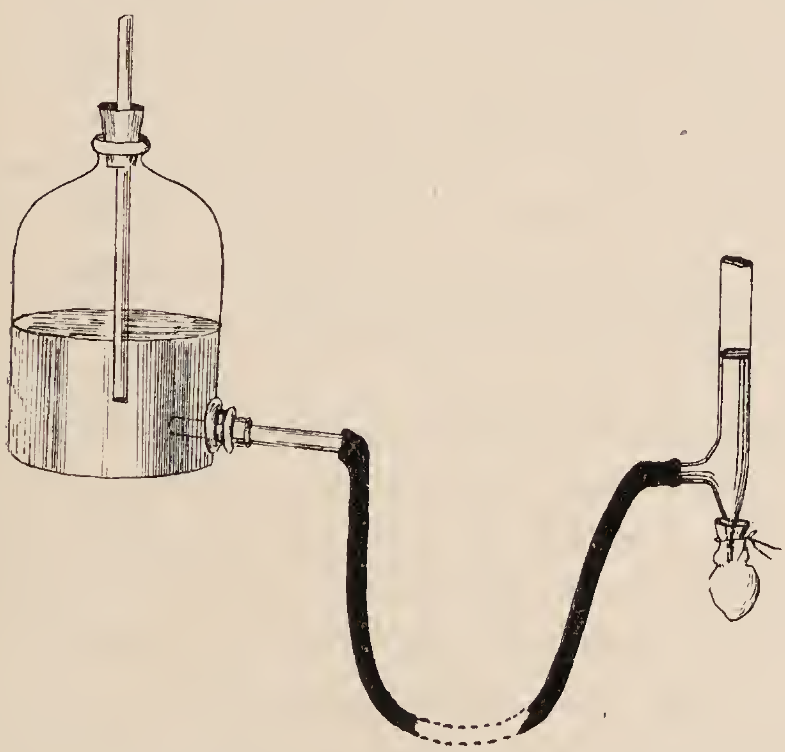


Fig. 81.—Diagram of apparatus for perfusion of frog's heart.

The perfusing fluid most commonly used is known as Ringer's fluid, and has the following composition :—

NaCl . . .	0·65 per cent.
KCl . . .	0·03 ,,
$CaCl_2$ . . .	0·02 ,,
A trace of sodium carbonate.	

If 0·1 per cent. dextrose is added to this solution, it is called Locke's fluid.

By means of this or similar methods, the influence of changes in the composition of the perfusing fluid upon the rate and force of the beat can be readily ascertained. The muscle of the frog's heart possesses a large store of energy, and will continue to beat for a long time without any fresh supply of nutrient material so long as the perfusing fluid contains oxygen. The force of the beat is dependent, however, not only on the oxygen supply, but also on the presence or absence of certain salts and on the reaction of the perfusing fluid.

(1) If the heart is perfused with a solution free from calcium, the contractions of the ventricle gradually become feebler, and the heart soon stops in diastole. When calcium, but not potassium, is present, the ventricle after a short time fails to relax completely during diastole, and eventually may come to a standstill in a fully contracted state. The presence of both calcium and potassium, as, for example, in Ringer's fluid, seems to be essential for the maintenance of the normal beat.

(2) The heart is extremely sensitive to slight changes in the reaction, that is, the H ion concentration, of the perfusing fluid. It beats most forcibly when the perfusing fluid is neutral; if the fluid is made slightly acid or slightly alkaline, the beats become smaller.

In the mammal the heart receives its blood supply through the coronary arteries, along which blood is flowing during both systole and diastole. The conditions which modify the supply of blood to the heart by the coronary vessels can be readily studied in the heart-lung preparation (p. 199). In the first place, the amount of blood flowing through the coronary vessels varies directly with the blood pressure in the aorta. Secondly, it is increased by the addition of adrenalin to the circulating blood, this substance dilating the coronary vessels. Thirdly, carbonic acid and other metabolic products of muscular activity dilate the coronary vessels. By one or other of these means the blood supply to the heart is increased whenever it does more work.

Ligature of a coronary artery, or of one of its main branches, is followed almost immediately by stoppage of the ventricles, and the heart cannot be made to beat again.

The force of the mammalian heart beat is also influenced by changes in the reaction of the blood. If the tension of carbonic acid in the blood is greatly increased, the heart relaxes more completely during diastole and contracts less forcibly during systole, with the result that its output is diminished. A decrease in the tension of carbonic acid, on the contrary, leads to the accumulation of blood in the great veins, less blood enters the heart during diastole, and the output of the heart is diminished.

Both in the frog and in the mammal, the rate of the heart is increased by a rise and decreased by a fall in the temperature of the fluid circulating through it. With this exception, changes in the character of the blood have little or no effect on the rate of the heart beat.

SECTION V.

THE REGULATION OF THE VASCULAR MECHANISM.

In order that the various tissues of the body may receive an adequate supply of nutritive material and oxygen, it is essential that the blood supply to the different organs should be varied in accordance with their needs. This end is attained by means of the central nervous system, which can modify the rate of the heart and the calibre of the arterioles in response either (1) to external stimuli, or (2) to impulses arising in the different parts of the body itself, or (3) to changes in the character of the circulating blood. This latter factor also directly influences the force of the heart beat and the calibre of the vessels.

THE INNERVATION OF THE HEART.

The nerves supplying the heart are (1) the vagus, and (2) branches from the sympathetic system. The sympathetic fibres arise in the frog from the white ramus of the third spinal nerve, and have their cell station in the corresponding sympathetic ganglion. From the ganglion they pass upwards to join the vagus close to its exit from the skull; the combined vagus and sympathetic fibres form a single nerve on each side, the vago-sympathetic, which runs to the heart (fig. 82). The fibres of the vagus nerve have their cell station in the ganglia of the heart itself.

In the mammal the vagus gives off branches in the thorax, which run direct to the heart, in which their cell stations lie. The sympathetic fibres leave the spinal cord by the second and third thoracic white rami; their cell stations are in the stellate ganglion, from which post-ganglionic fibres run directly to the heart.

The Vagus.—When a weak stimulus is applied to the peripheral portion (*i.e.* the end towards the heart) of the divided vago-sympathetic nerve in the frog, the heart immediately beats more slowly: a stronger stimulus brings the heart to a standstill. When the stimulus ceases, the heart begins to beat again, at first feebly, but soon more strongly than before the stimulus was applied. This effect of the vagus is known as "inhibition," since the nerve, when stimulated, checks or inhibits the normal rhythm of the heart.

In the mammal, stimulation of the peripheral end of the vagus produces the same effect, and, if the blood pressure is being recorded,

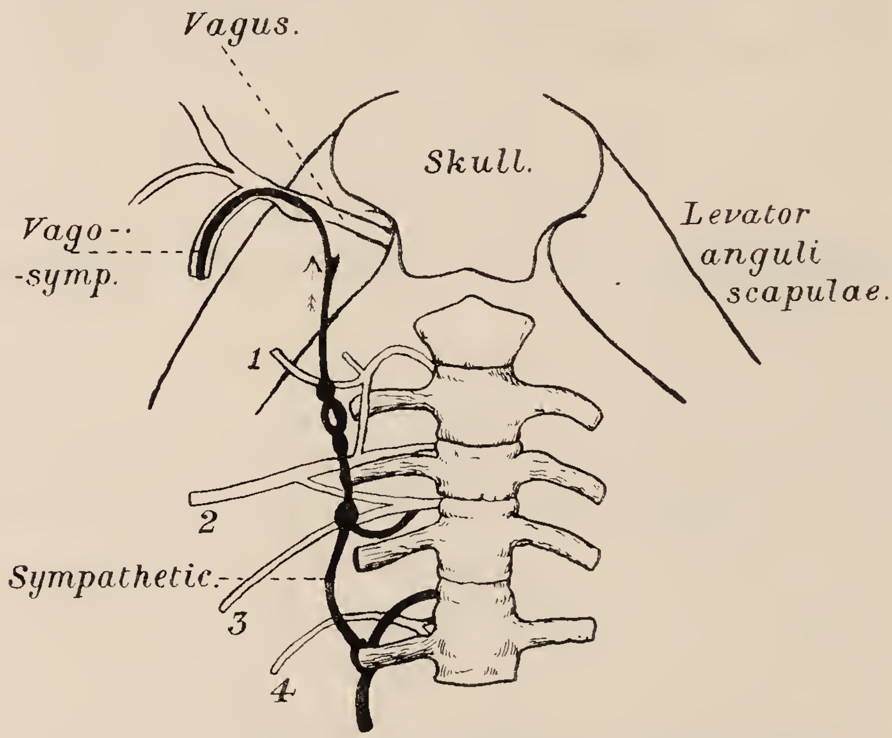


Fig. 82.—Origin of the nerves to the frog's heart.
1, 2, 3 and 4 are spinal nerves.

the tracing shows a marked fall of pressure (fig. 83). When the stimulus is removed, the heart begins to beat again, and the blood pressure returns to, or even rises above, its original level. Sometimes, especially if the stimulus is prolonged, the ventricle may again begin to beat slowly even during the stimulation. This phenomenon is known as "vagus escape," and is due to the fact that the ventricle is beginning to beat independently with its own normal slow rhythm.

In the frog the vagus fibres supply not only the sinus and auricles, but also the ventricle. In many, and probably in all mammals, the vagus fibres are distributed to the auricles, but not to the ventricles; stimulation of the vagus in this case affects only the auricles directly, and the ventricles stop beating because they no longer receive the normal stimulus from the auricles. As a rule the vagus affects chiefly the sino-auricular node, inhibiting the impulses normally originating at this point, and the whole heart is brought to a standstill. Occasionally

it seems to act mainly by lessening the conductivity of the bundle of His, and the auricles continue to beat at their usual rate, whereas the ventricles beat infrequently or not at all.

The Sympathetic Fibres.—Stimulation of the sympathetic nerves, either in the frog or in the mammal, quickens the heart, and for this reason they are called accelerator nerves; usually the force of the heart

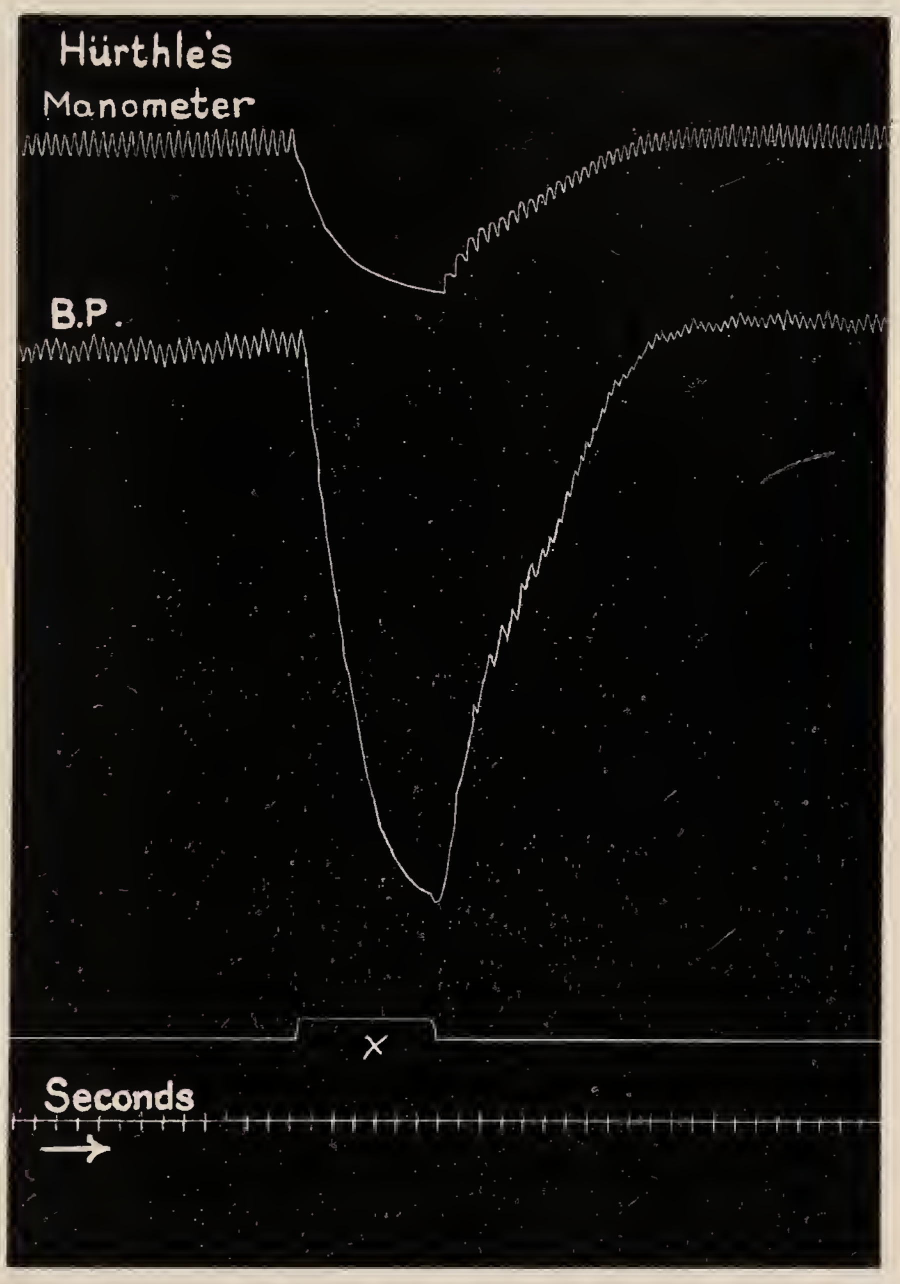


Fig. 83.—Stimulation of peripheral end of one vagus at X.
Note the inhibition of the heart and fall of blood pressure. B.P., arterial pressure recorded by mercurial manometer.

is also increased. The effect is only produced after a latent period of some seconds, and lasts for a little time after the cessation of the stimulation (fig. 84). In the mammal the blood pressure may rise slightly or may be unaffected.

Cardiac Reflexes.—The efferent fibres of the vagus arise from a collection of nerve cells lying in the medulla oblongata, and known as the vagus centre. Impulses are constantly passing from the centre down the vagus; these exert a restraining force on the rate of the heart beat and tend to inhibit it. This action of the vagus centre is

described as its *tonic* inhibitory action, and is particularly well marked in the dog and horse. On section of the vagus nerves the tonic action is abolished and the heart beats more rapidly. The tone of the vagus

FIG. 84.—Upper tracing shows acceleration of the heart due to stimulation of an accelerator nerve.

centre can be reflexly increased or diminished by afferent impulses reaching it from various parts of the body. The most important afferent paths are (1) the depressor nerve, (2) afferent fibres running in

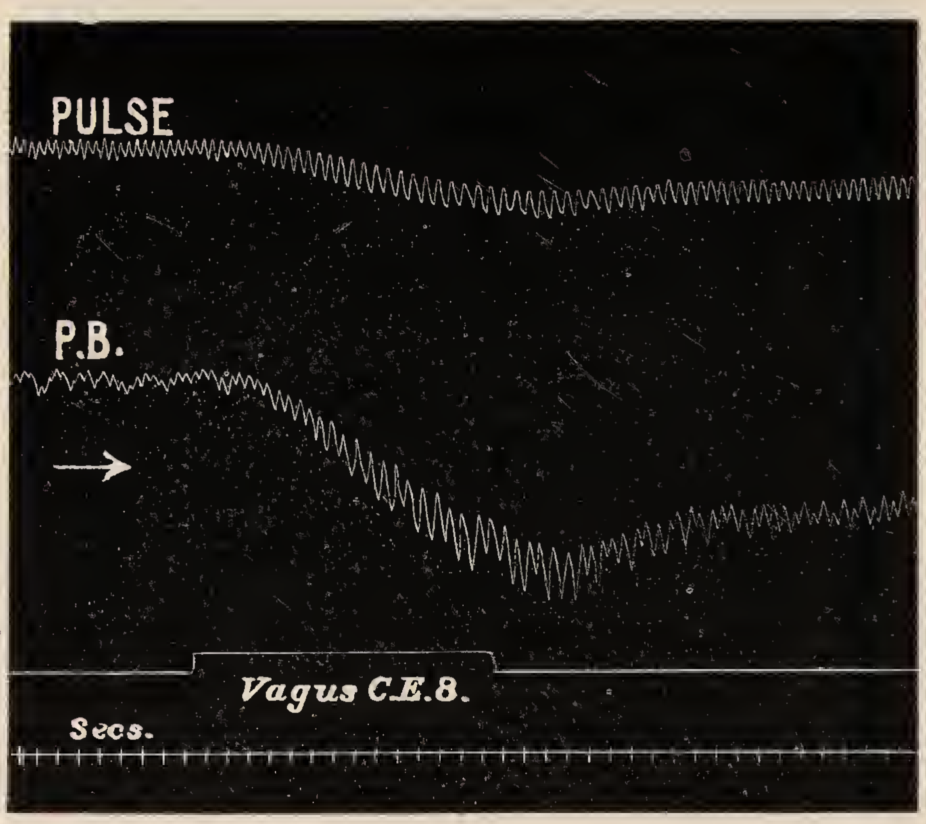


FIG. 85.—Reflex slowing of the heart due to stimulation of central end of one vagus. The other vagus is intact.

the vagus from the lungs and from the heart itself, and (3) many sensory nerves.

(1) **The depressor nerve** is purely afferent, and, starting in the walls of the aortic arch, it runs up the neck on each side, in some animals (rabbits) as a separate nerve, in others bound up with the

vagus trunk, to end in the medulla oblongata. If the nerve is divided, stimulation of its central portion (*i.e.* the end towards the brain) causes a fall of blood pressure and slowing of the heart. The slowing of the heart is due to a reflexly produced increase of vagus tone, and does not occur when the depressor nerve is stimulated after section of the vagi.

(2) Stimulation of the central end of one vagus usually causes slowing of the heart, provided the other vagus is intact (fig. 85).

(3) The stimulation of the central end of almost any sensory nerve, which in a conscious animal would give rise to pain, causes reflex

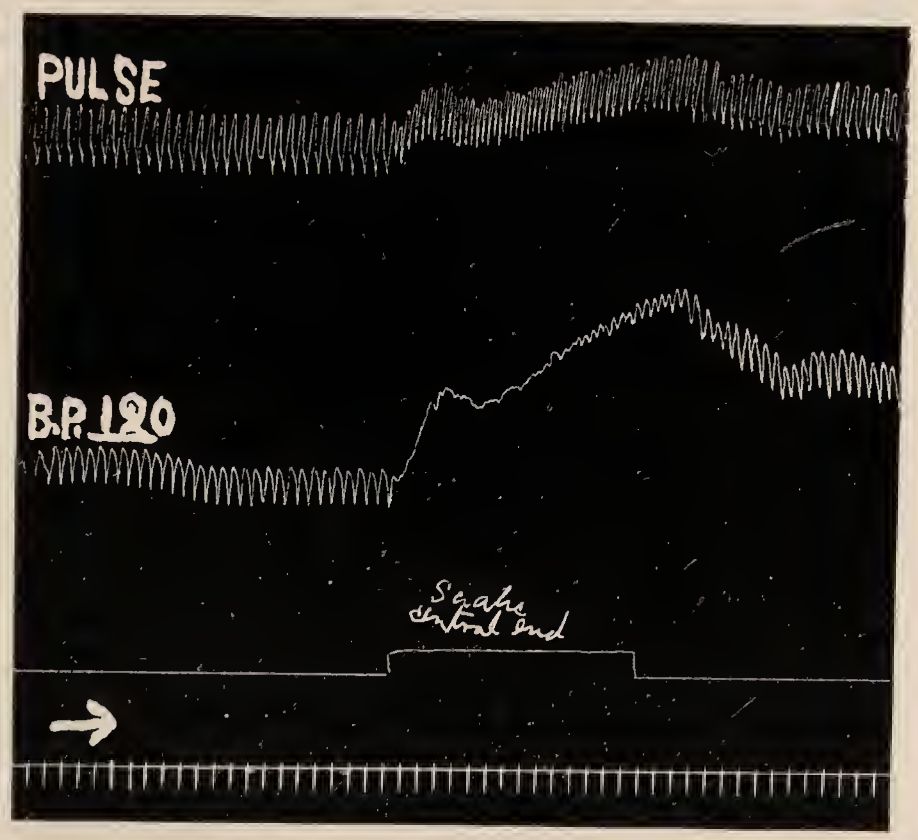


Fig. 86.—Reflex acceleration of the heart and rise of blood pressure caused by stimulation of central end of the (divided) sciatic nerve.

quickening of the heart (fig. 86), owing mainly to diminution of the tone of the vagus centre and partly to stimulation of the accelerator nerves. Stimulation of the central end of the splanchnic nerves or of the fifth nerve, however, causes slowing of the heart, an effect which is sometimes seen to follow a severe blow on the abdomen, and which is also readily produced by irritation of the nasal mucous membrane.

The tonic action of the vagus centre is also increased when the general blood pressure is raised, and the heart is slowed, possibly as the direct effect of the increased blood pressure on the vagus centre. This relationship between the blood pressure and the pulse rate is known as Marey's law, which states that "the pulse rate varies inversely with the blood pressure." Exceptions to this law are observed (1) during muscular exercise and (2) as a result of painful stimuli.

The accelerator nerves also exert a tonic influence on the heart, tending to quicken it, and when they are divided the heart beats more slowly.

The rate of the heart is also modified by impulses passing to the vagus centre from the higher parts of the brain, the acceleration occurring during excitement, for example, being brought about by this means.

The Action of Drugs on the Heart.—The action of drugs on the heart is most easily studied in the frog. The rate of the heart beat is slowed by pilocarpine or muscarine, which stimulates the vagus endings in the heart, this effect being abolished by atropine, which paralyses these endings, so that after its administration stimulation of the vagi has no effect on the rate of the heart. Atropine has no action on the accelerator nerve endings. Nicotine first stimulates and then paralyses the cell stations of the vagus in the heart; and if it is painted on the heart, stimulation of the vagus is ineffective, since the impulses passing along it are blocked at the cell stations. Adrenalin stimulates the nerve endings of the accelerator nerve, thereby increasing both the force and the frequency of the heart beat.

THE INNERVATION OF THE BLOOD-VESSELS.

The Vaso-constrictor Nerves.—If the ears of a rabbit, preferably a light coloured one, are examined, it will be observed that when one cervical sympathetic nerve is divided, the ear on that side almost immediately becomes flushed. The central artery and its branches can be seen to become wider, many small vessels previously invisible come into view, and the whole ear becomes warmer than the opposite one. Stimulation of the peripheral end of the cervical sympathetic nerve causes an immediate constriction of the blood-vessels, many of which disappear from view, and the ear becomes paler and cooler than that of the opposite side.

This experiment, which was first carried out by Claude Bernard, shows that the cervical sympathetic nerve contains fibres which run to the blood-vessels of the ear, and which, when stimulated, cause constriction of the arterioles by the contraction of their muscular walls. It proves, further, that normally the muscular coats of the arterioles are neither fully relaxed nor fully contracted, but are in a state of partial contraction, which is spoken of as *tone*. The tone of the arterioles exists only so long as they are in connection with the central nervous system, and is dependent upon impulses passing from the nervous system. The nerve fibres which carry these impulses to the arterioles, and which when stimulated increase their tone, causing them to constrict still further, are called *vaso-constrictor* nerves.

In other organs the presence of vaso-constrictor nerves, and the

effect of section or stimulation of these nerves on the calibre of the arterioles has been ascertained, not by direct ocular observation, but by determining the amount of blood flowing through the organ in a given time. The volume of blood (V) flowing through an organ in a given time varies directly with the mean arterial pressure (P) and inversely with the resistance (R) in its arterioles, and is represented by the formula $V \propto \frac{P}{R}$. Hence the rate of blood flow through a small organ such as the kidney may be altered in one of two ways. On the one hand, in the absence of any active change in its arterioles, a rise of the general arterial blood pressure will force more blood through the arterioles of the kidney. On the other hand, if the general pressure remains constant, dilatation of the renal arterioles will lead to an increased rate of blood flow through the kidneys by lessening the resistance to the flow of blood. In experiments on the rate of blood flow through an organ it is necessary, therefore, to record both the rate of flow and the general arterial pressure, in order to ascertain whether the alterations in flow are due to local changes in the arterioles, or to changes in the general arterial pressure, or possibly to a combination of these factors.

The amount of blood flowing from an organ in a given time may be directly measured by allowing the blood escaping by the veins to pass along a graduated tube. Thus if 2 c.c. of blood flow into the tube in 4 seconds, the rate of flow is 30 c.c. per minute. This method is very useful in the case of small organs such as the kidney or submaxillary gland.

Another method is to record the variations in volume of the organ. These variations depend almost entirely upon the amount of blood present in the organ at any moment, and this will alter with the degree of dilatation or constriction of its blood-vessels. The organ is placed in an air-tight box or instrument known as a *plethysmograph*, provided with a small opening which is connected with a tambour and a recording lever. When the organ expands, the air in the box is driven along the tube into the tambour, thereby raising the lever; shrinkage of the organ has the opposite effect. The form of plethysmograph varies with the shape of the organ which is being studied. The one generally used for the kidney, and known as an oncometer, is made of vulcanite with a glass lid; in one side is a groove through which the renal vessels and nerves can pass (fig. 87). The box is made air-tight by filling the interstices with vaseline. A glass tube passing through its wall is connected with a piston recorder (p. 199). Fig. 88 represents a record of the kidney volume thus obtained, simultaneously with a

general blood-pressure tracing, and shows the effect of stimulating the peripheral end of a divided renal nerve.

By one or other of these methods it is found that division of the nerves passing to the kidney produces an increase of its volume and an increased flow of blood through it, whereas stimulation of the nerves has the opposite effect. Since in these experiments the general arterial pressure remains practically unaltered, the changes in the rate of blood flow produced by section or stimulation of the renal nerves must be brought about by alterations in the calibre of the arterioles of the kidney.

FIG. 87.—Oncometer.

Experiments of this kind show that the arterioles of almost every organ in the body are supplied with vaso-constrictor nerves. The tone

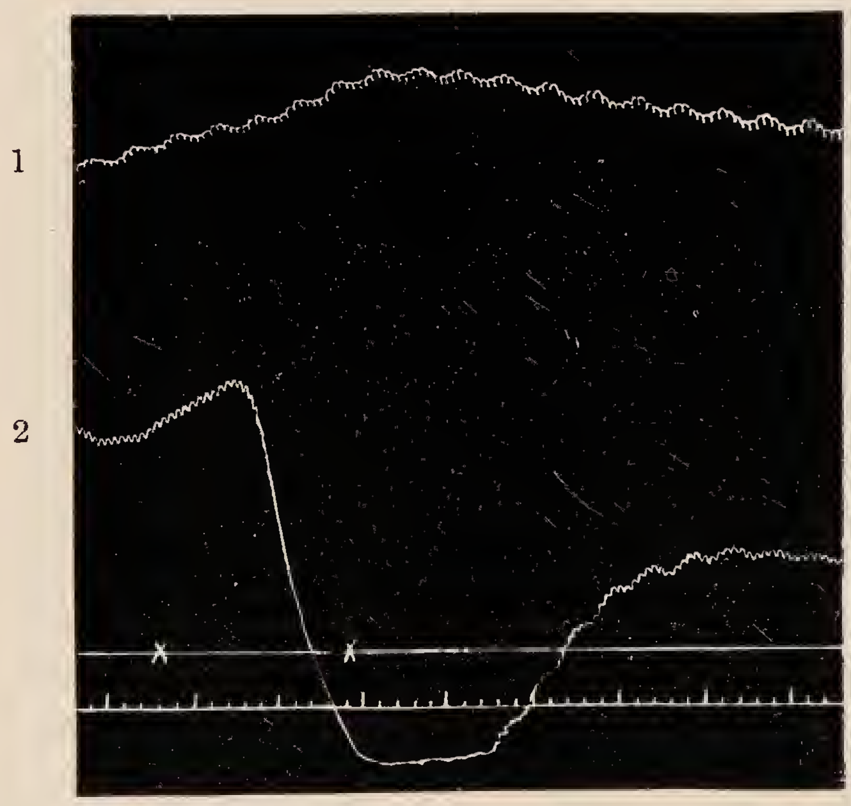


FIG. 88.—Tracing of arterial blood pressure (1), and kidney volume (2). Between X and X the 10th thoracic nerve-root was stimulated, causing a decrease in kidney volume. (From *Practical Physiology*, by Pembrey and others.)

of these vessels is controlled by a centre, the *vaso-motor centre*, lying in the medulla oblongata; nerve fibres pass from the cells of this centre down the spinal cord, to end in all probability round cells in the lateral horn in the dorsal region and round corresponding cells in the lumbar region. These cells give off small medullated fibres, which leave the spinal cord by the anterior roots and enter the white rami

communicantes to form part of the sympathetic system; their subsequent course has already been described (p. 101).

The mean arterial pressure is determined largely by the resistance offered by the arterioles to the flow of blood through them; it rises when they constrict, and falls when they dilate. Hence stimulation of the vaso-motor centre by causing constriction of arterioles all over the body produces an enormous rise of blood pressure; destruction of the centre is followed by dilatation of the arterioles, and the blood pressure falls to 40 mm. Hg or less. The centre lies in the floor of the fourth ventricle, its lower limit in the rabbit being about 4 mm. above the apex of the calamus scriptorius, and its upper limit about 4 mm. higher. Its position has been ascertained experimentally by observing the effect on the blood pressure of transection of the brain-stem at various levels. Section through the pons or upper part of the medulla oblongata does not affect the blood pressure; when the section passes through the upper end of the centre it produces a slight fall of pressure, and if a section is made a few millimetres lower the fall of pressure is maximal. On division of the spinal cord in the cervical region, all the arterioles are cut off from the vaso-motor centre, and the fall of blood pressure is as great as after destruction of the centre itself. When the transection is made in the dorsal region, only those arterioles which receive vaso-constrictor nerves from the spinal cord below the lesion will lose their tone; and the fall of arterial pressure becomes less marked the lower the level at which the spinal cord is divided, transection in the lower lumbar region having no effect upon the mean arterial pressure.

If an animal is kept alive for some hours or days after transection of the spinal cord, its arterioles gradually recover their tone and the blood pressure returns to a normal level. This is brought about by means of subsidiary vaso-motor centres in the spinal cord, which are called into play when the medullary centre is put out of action. On subsequent destruction of the spinal cord, the blood pressure falls almost to zero.

The only arterioles in the body which are not known to be influenced by vaso-constrictor nerves are the cerebral and coronary vessels. Recent observation has shown that, contrary to the views formerly held, vaso-motor fibres are distributed to the pulmonary vessels; their existence has been demonstrated by means of adrenalin (p. 234), which stimulates the endings of the vaso-constrictor fibres and produces constriction of the arterioles. The addition of adrenalin to the blood flowing through the lungs is followed by constriction of the pulmonary arterioles and a rise of pressure in the pulmonary artery, and if the lungs are perfused under a constant pressure the outflow of blood is diminished.

The Vaso-Dilator Nerves.—In many parts of the body the arterioles are supplied not only with vaso-constrictor but also with vaso-dilator nerves, stimulation of which produces dilatation of these vessels owing to relaxation of their muscular walls. The chorda tympani nerve, for example, sends vaso-dilator fibres to the vessels in the sub-maxillary gland, and when it is stimulated the blood flow through the gland is increased, and may become four or five times as large as that taking place before stimulation of the nerve. Since the general blood pressure remains unaltered, this increase in the blood flow through the gland must be due to dilatation of its arterioles. Vaso-dilator fibres are also found in the nerves supplying the other salivary glands, the tongue, and other structures in the head. Similar fibres leave the spinal cord by the anterior roots of the second and third sacral nerves, and stimulation of these nerves, which are called the nervi erigentes, causes dilatation of the blood-vessels of the generative organs and the rectum.

The vaso-dilator nerves show two important points of difference from the vaso-constrictor nerves. In the first place, mere section of the nerves produces no obvious effect upon the calibre of the blood-vessels, so that, unlike the vaso-constrictors, the vaso-dilator fibres do not appear to exercise a continuous influence upon the tone of the arterioles. Secondly, the cell stations for these nerves lie, not in the sympathetic ganglia, but close to or even within the organ whose arterioles they supply.

In the instances just given the nerves contain only vaso-dilator fibres, but in the nerves supplying the limbs both vaso-dilator and vaso-constrictor fibres are present. Stimulation of the peripheral end of a nerve, such as the sciatic, usually causes vaso-constriction, though the existence of vaso-dilator fibres can be demonstrated in one of the following ways:—

(1) If the sciatic nerve is divided and its peripheral end stimulated immediately, the arterioles constrict, but when the nerve is stimulated two or three days after section, the arterioles dilate. This result is due to the fact that the constrictor fibres degenerate and cease to carry impulses earlier than do the dilator fibres.

(2) If the sciatic nerve is stimulated with single induction shocks repeated at intervals of one to two seconds, these shocks stimulate only the dilator fibres, and the arterioles dilate.

(3) The dilator nerves are excited more readily than the constrictor nerves by mechanical stimuli, such as pinching the nerve.

The constriction or dilatation of the arterioles, thus produced, decreases or increases the amount of blood flowing through the vessels of the limb, and alters the volume of the limb. These changes in volume

can be readily recorded by enclosing the distal part of the limb in a plethysmograph of suitable shape, which is connected with a tambour and a recording lever.

Bayliss has shown that the vaso-dilator fibres to the limbs leave the spinal cord by the posterior roots, and that stimulation of the peripheral

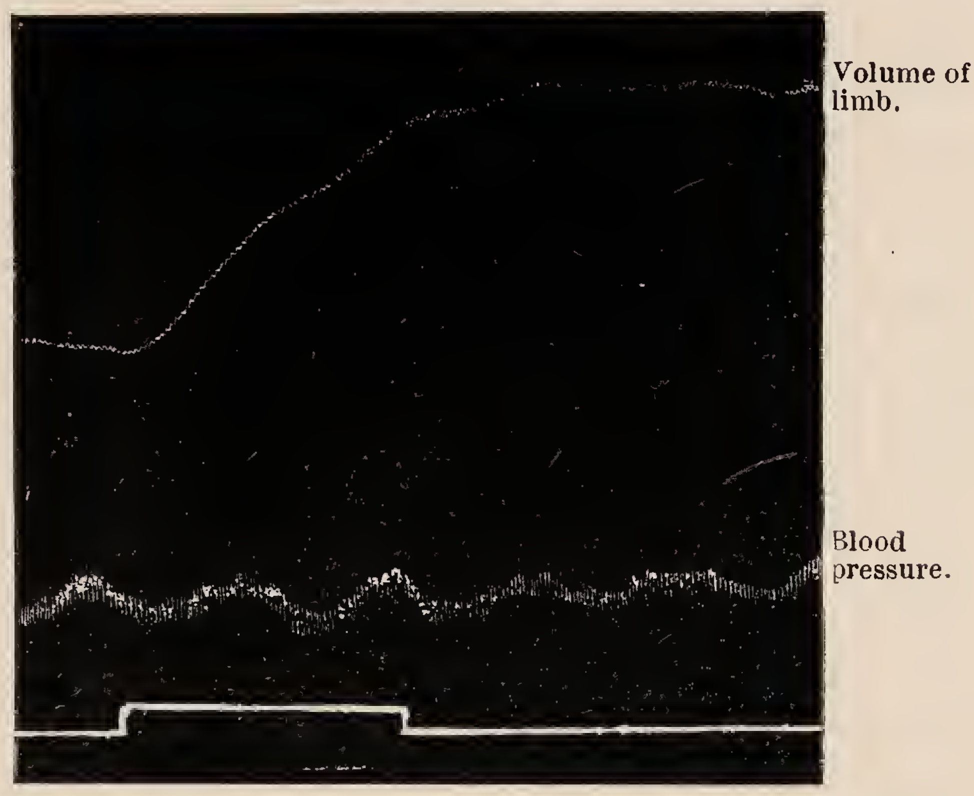


Fig. 89.—Stimulation of peripheral end of 7th lumbar posterior root. (Bayliss.)

end of the posterior roots causes marked dilatation of the arterioles (fig. 89). The posterior root fibres starting in the skin and deep tissues normally carry impulses from these structures to the spinal cord and brain. When stimulation of the peripheral end of the

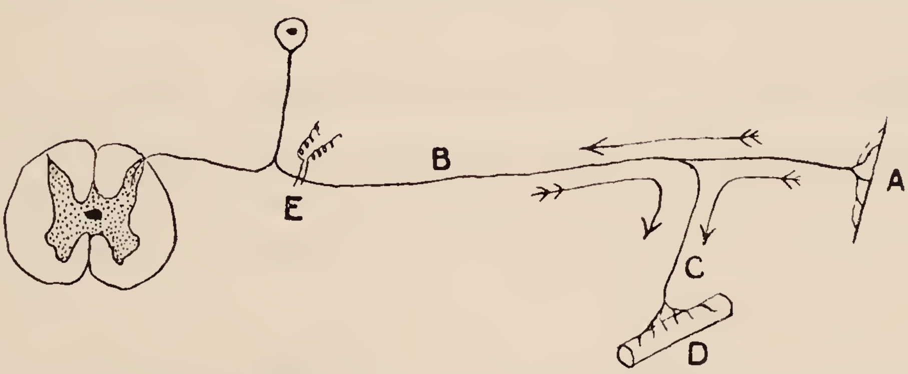


Fig. 90.—Scheme to show path of antidromic impulses (axon reflex).

posterior root causes dilatation of the arterioles, the impulses must pass towards the periphery, that is, in the opposite direction to that taken by the impulses from the skin. For this reason the impulses running towards the periphery and causing vaso-dilatation have been called *antidromic*. In normal circumstances a stimulus applied to the skin at A (fig. 90) will give rise to an impulse passing along the

sensory nerve B into the spinal cord; in its course each nerve fibre gives off a branch C, which ends in the walls of the arterioles (D) of the limb. The impulse passing along the fibre B also passes along C and relaxes the muscle of the arterioles. Since nerve fibres can conduct impulses in both directions, stimulation of the posterior root fibres at E gives rise to an impulse which, travelling down the nerve, passes by the branch C to the arterioles at D, and causes them to relax. We see, therefore, that whether the stimulus is applied at the periphery A or at E, the impulse reaches the arterioles along the branch C. The effect of stimulation at A, which is not a true reflex, is called an *axon reflex.* If the posterior root fibres become degenerated peripherally to the ganglion, the axon reflex disappears, and a stimulus applied to the skin at A causes no dilatation of the subcutaneous vessels.

This reflex is of great importance to the body. As is well known, an irritant (*e.g.* a mustard blister) applied to the skin causes dilatation of the cutaneous vessels and reddening of the skin. The dilatation of the vessels is part of the means by which the tissues protect themselves against injuries or irritants, and if the vascular changes do not occur, owing to degeneration of the peripheral sensory fibres, the damage done by the irritant to the tissues may be much more severe.

Vaso-dilator fibres are also present in the sympathetic system itself, although their presence is not readily demonstrated owing to the greater abundance of vaso-constrictor fibres; but when the endings of the latter are paralysed by the drug ergotoxin, stimulation of the splanchnic nerves causes vaso-dilatation and a fall of blood pressure.

The vaso-dilator fibres seem to be concerned mainly, though not entirely, with bringing about an increased flow of blood in individual organs, whereas the vaso-constrictor fibres, controlled by the vaso-motor centre, regulate the tone of the arterioles of the body as a whole.

Influences Affecting the Vaso-motor Centre.—The vaso-motor centre is extremely susceptible both to impulses reaching it from other parts of the nervous system, whether these reach it from the higher parts of the brain or from the peripheral nerves, and to changes in the character and amount of the blood passing to the brain. Its activities are constantly varying in response to these stimuli, in such a way that the mean arterial pressure is raised to meet special needs of the body, and is prevented from falling below the level necessary for the adequate supply of blood to the tissues, and more especially to the brain.

(1) *Nervous Stimuli.*—The depressor nerve is a purely afferent nerve, originating in the root of the aorta, and passing to the brain. Electrical stimulation of its central end causes a lessening of the activity of the vaso-motor centre, decrease of the tone of the arterioles, and a

fall of blood pressure; this occurs whether the vagus nerves have been previously divided or are intact. In all probability, when the arterial blood pressure is very high, impulses are set up in the endings of the nerve in the stretched aortic wall which reflexly lower the blood pressure, and thus lessen the strain placed upon the heart. The passage of impulses along the depressor nerve in these circumstances can be observed by means of the string galvanometer.

Increased activity of the centre and a rise of blood pressure are brought about by stimulation of most sensory nerves (see fig. 86), and also by impulses passing to it from the cerebral cortex during muscular exercise and in violent emotional excitement, such as fear or anger.

(2) *The Composition of the Blood.*—The vaso-motor centre is extremely sensitive to changes in the composition of the blood supplying it, being stimulated by lack of oxygen or by the presence of an excess of carbonic acid in the blood. The effect of lack of oxygen and of excess of carbonic acid is seen in its most extreme form in asphyxia (p. 270), but even a slight excess of carbonic acid stimulates the centre, and leads to constriction of the arterioles and a rise of blood pressure. The same effect is produced when the reaction of the blood, measured by its H ion concentration, becomes less alkaline; and the injection into the blood stream of small amounts of an acid, such as lactic acid, may produce a considerable rise of blood pressure. Further, the vaso-motor centre is stimulated whenever the amount of blood passing through the brain in a given time diminishes.

During asphyxia the blood-pressure tracing often shows, in addition to the oscillations caused by the heart beat, two other groups of waves. In the first place, the blood pressure shows oscillations corresponding with the respiratory movements; they are still present in a curarised animal, and are due to impulses passing by irradiation from the excited respiratory centre to the vaso-motor centre. They are called Traube-Hering curves. Secondly, much larger waves, known as Mayer curves, are seen, and are due to rhythmical variations in the activity of the vaso-motor centre; they are often present after severe hæmorrhage.

The subsidiary vaso-motor centres, unlike the chief centre, are extremely insensitive to either nervous or chemical stimuli, and probably they take little or no part in the vascular changes normally occurring in the body, though their activity can be excited by asphyxia.

In whatever way the activity of the vaso-motor centre is increased, the constriction of the blood-vessels which is produced is most pronounced in the abdominal organs. The splanchnic nerves send constrictor fibres to the blood-vessels of almost the whole of the abdominal

viscera, and the total capacity of these vessels is so large that the amount of blood contained in them forms a great proportion of the total blood in the body. Further, the general arterial pressure is more markedly altered by section or stimulation of the splanchnic nerves than of any other nerve in the body.

Hence the maintenance of the mean arterial pressure at a constant level, in spite of the varying influences which are brought to bear upon the vaso-motor centre in daily life, is largely effected by changes in the degree of constriction of the arterioles supplied by the splanchnic nerves, and known as the splanchnic area. For example, when the depressor nerve is stimulated, the fall of pressure which occurs is due mainly to the dilatation of the arterioles in the splanchnic area. When the blood supply to the centre is deficient, the resulting rise of blood pressure is caused primarily and chiefly by constriction of the arterioles of the abdominal organs. During muscular exercise an increased flow of blood through the skeletal muscles is required and takes place, and the vessels in the splanchnic area are constricted, more blood being diverted into the muscular system. On the contrary, during digestion the digestive organs require an abundant blood supply, and the vessels of the skin are contracted, while the arterioles of the digestive tract are relaxed. It is for this reason that severe exercise taken immediately after a meal tends to disturb digestion.

When the arterioles of the abdominal organs constrict in response to stimulation of the splanchnic nerve, they naturally contain less blood than before, and the blood thus squeezed out of them by their constriction has to be accommodated in other parts of the vascular system. Much of it passes into the arteries, thereby distending them more fully, and so raising the arterial pressure. This factor is an additional cause of the rise of blood pressure which is brought about by stimulation of the splanchnic nerves.

Influence of Gravity on the Circulation. — If a thin-walled, cylindrical rubber bag is filled with fluid and held with its long axis vertical, the fluid, under the influence of gravity, tends to accumulate at, and to distend, the lower end of the bag. In the body also, the blood tends to accumulate in the most dependent parts, and if a rabbit is held up by its ears the blood accumulates in the abdominal area, particularly in the large veins, and the arterial blood pressure falls (fig. 91). As a result, the amount of blood passing through the brain in a given time is inadequate, and its functions are seriously interfered with, so much so that it is said to be possible to kill a hutch rabbit by holding it up in this position for a short time, death being due to anæmia of the brain.

The influence of gravity is antagonised completely in man, and to a lesser extent in most animals, by means of a compensating action on the part of the vaso-motor centre. When a man rises from the horizontal to the standing position, the blood tends to accumulate in his abdomen, and the supply of blood to the brain is diminished. This diminution at once stimulates the extremely sensitive vaso-motor centre, which sends out impulses constricting the arterioles of the splanchnic area, thereby forcing the blood out of this area into the rest of the body, including the brain. Conversely, the splanchnic arterioles

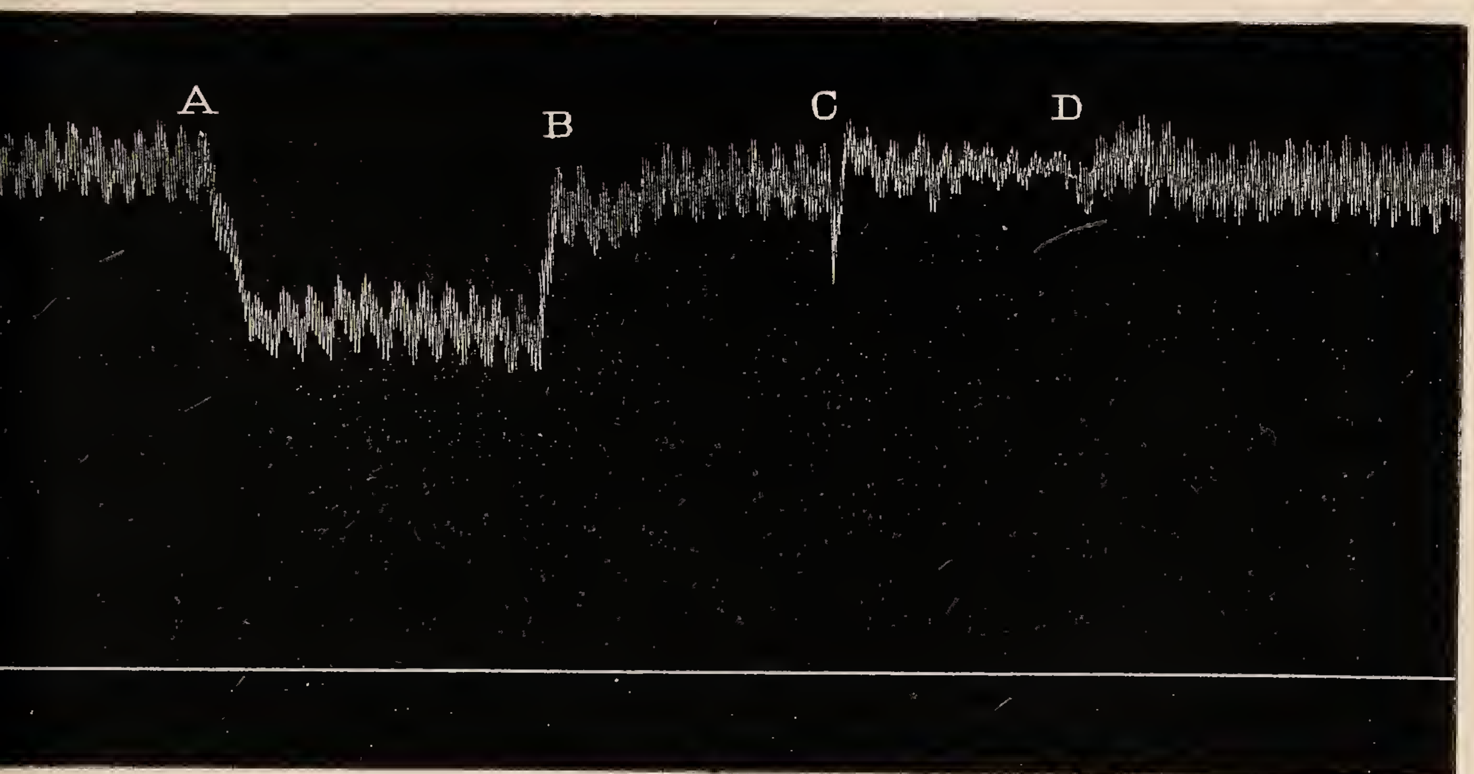


FIG. 91.—Aortic blood pressure. Effect of posture. (L. Hill.) From *Practical Physiology*, by Pembrey and others.

A–B, vertical, head up; B, horizontal; C, vertical, head down; D, horizontal.

relax to some extent whenever an individual changes from the vertical to the horizontal position.

This reaction on the part of the vaso-motor centre to any change in the position of the body as regards gravity, is so rapid and complete that we are not normally aware of its existence. The temporary giddiness, which is often noticed by individuals who are anæmic or run down on changing suddenly from a horizontal to a standing position, is due to the fact that the response of the vaso-motor centre to the change of position is slower than usual, and that for a few moments the brain is inadequately supplied with blood. In the same way "fainting" is in many cases caused by temporary diminution of the activity of the vaso-motor centre, so that the blood pressure falls and the blood supply to the brain is deficient, causing loss of consciousness. The

compensating action of the vaso-motor centre for the effects of gravity is also inefficient in anæsthetised persons.

Owing to the influence of gravity, the arterial pressure in the femoral artery of an individual in the erect position is much higher than that in the brachial artery. The constriction of the arterioles of the legs, however, is so great that the pressure in the capillaries and veins of the leg and foot is no higher than that in the hands. The flow of blood from the foot and leg back to the heart against the force of gravity is greatly assisted, and indeed made possible, by muscular movement: each muscular movement squeezes the blood along the veins towards the heart, and the valves prevent any reflux. In persons who are compelled to stand still for any length of time, or in whom the valves are defective, the veins tend to become dilated and varicose.

The Effect of Hæmorrhage.—Any considerable loss of blood from the body lessens the amount present in the arterial system, and the output of the heart at each beat decreases; the arterial pressure falls, and the supply of blood to the brain becomes inadequate. The vaso-motor centre is at once stimulated, causing increased constriction of the arterioles; at the same time fluid passes from the tissues into the blood, and the arterial pressure rapidly regains its normal level. After a very severe hæmorrhage these compensatory mechanisms are inadequate, and the blood pressure remains low.

The Influence of Adrenalin.—The structure and functions of the suprarenal glands are dealt with on p. 400, but it is necessary to mention at this point their influence on the circulation. These glands produce a substance, adrenalin, which can be extracted from them and obtained in a pure form. A minute amount of adrenalin (*e.g.* 0·01 or 0·02 mgr.), injected into a vein, stimulates the nerve endings of all the fibres of the sympathetic system, including those which supply the arterioles, and causes extreme vaso-constriction of all the arterioles except the coronary vessels, which are dilated, and the cerebral vessels, which are unaffected; and if the vagus nerves have been divided a huge rise of blood pressure is produced. The suprarenal glands receive fibres from the splanchnic nerves, and when a splanchnic nerve is stimulated, some of the adrenalin present in the suprarenal gland passes into the suprarenal vein and so into the blood stream, and gives rise to the effects just described. It is clear, therefore, that whenever a splanchnic nerve is stimulated the ensuing rise of blood pressure is partly due to the increased peripheral resistance brought about by the direct action of the splanchnic nerve on the abdominal blood-vessels, and is partly caused by the constriction of arterioles all over the body by the adrenalin set free into the blood stream. The influence of

these two factors is seen in the form of the blood-pressure tracing, which often shows, as it rises, a small notch or step (fig. 92); the first part of the rise is due to the direct action of the splanchnic nerve; the rise above the notch is due to adrenalin. Owing to the setting free of adrenalin, stimulation of a splanchnic nerve causes diminution in the volume of the limbs. These effects are produced not only when the splanchnic nerve is divided and its peripheral end is directly stimulated, but also when the impulse passing along the splanchnic nerve originates in the vaso-motor centre itself, as in asphyxia. After extirpation of the suprarenal glands, adrenalin can no longer be set free into the blood stream, and stimulation of the splanchnic nerve causes a much smaller rise of blood pressure; the vaso-constriction is limited to the abdominal vessels, and the blood-vessels of the limbs are passively dilated by the higher arterial pressure (fig. 93).

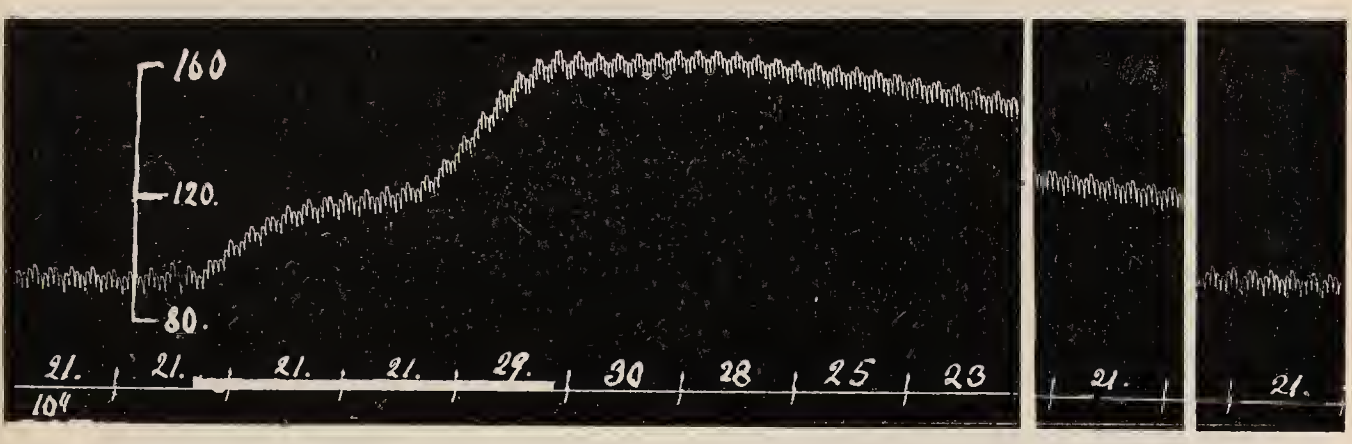


FIG. 92.—Blood-pressure tracing, showing effect of stimulation of left splanchnic nerve. (von Anrep.)

Shock.—After severe injuries or profuse hæmorrhage an individual may pass into the condition known as shock. The characteristic symptoms of shock are a low arterial blood pressure, and disappearance of many of the normal reflexes; the pulse is rapid and feeble, the respiration is shallow, and the temperature is low. A similar condition sometimes occurs after surgical operations, and can be experimentally produced in animals. Its causation is not understood, though various explanations have been offered to account for the low blood pressure, which forms such an important part of shock. The low blood pressure is not due to paralysis of the vaso-motor centre, since the centre responds to afferent stimuli almost as readily as in the normal animal. It has been suggested that in shock the veins dilate and that the blood accumulates in them, leaving the arterial system comparatively empty: in these circumstances the arterial pressure will be low, and the nutrition of the brain will be impaired. Other explanations have also been offered, none of which is entirely satisfactory.

Local Changes in the Arterioles.—The variations in the activity of the vaso-motor centre, brought about by the means already described, are chiefly directed to regulating the mean arterial pressure and to providing an efficient supply of blood to the brain. Alterations in the calibre of the arterioles in any one organ of the body as distinct from the body in general are sometimes due to the presence of vaso-dilator nerves, as, for example, the chorda tympani. There is, however, another factor of great importance. Generally speaking, increased functional activity of any organ of the body is accompanied by dilatation of its arterioles and an increased flow of blood through it; this is brought

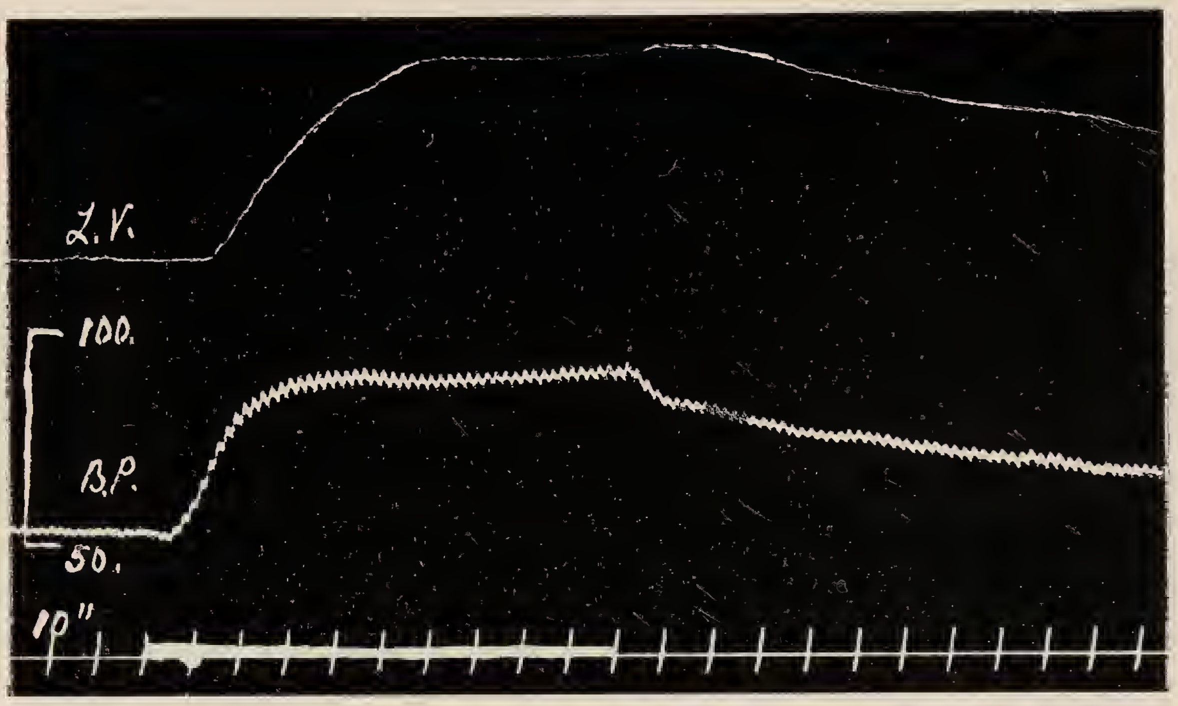


FIG. 93.—Stimulation of a splanchnic nerve after removal of the suprarenal glands. (von Anrep.)

L.V., volume of leg enclosed in a plethysmograph; B.P., arterial blood pressure.

about partly, or even wholly, by the direct action upon the walls of the arterioles of the waste products (metabolites) formed by the organ during its activity. They include carbonic acid, lactic acid, and probably other substances, and experiment has shown that when these products are added to the blood passing through an organ, *e.g.* the heart or skeletal muscle, its arterioles dilate. This local mechanism provides a means by which the increased demands of a tissue for nutritive material and oxygen, when it is active, are met by an increase in the amount of blood passing through it.

THE CEREBRAL CIRCULATION.

The circulation of the blood through the brain is peculiar in two respects. In the first place, the brain is enclosed in a rigid case, the skull, which it almost completely fills, and, secondly, there is at present no conclusive evidence that the arterioles of the brain are under the

control of the vaso-motor centre, although the existence of nerve plexuses round them has been observed histologically. The presence of cerebro-spinal fluid in the skull allows for a slight increase in the volume of the blood in the cerebral blood-vessels, since a rise of pressure within these vessels distends them to a certain extent, and forces some of the cerebro-spinal fluid out of the skull into the sheaths of the nerve trunks. Apart from this increase, which amounts only to 2 or 3 c.c., the amount of blood in the cerebral vessels cannot be increased, since the capacity of the skull is constant, and the brain, which, together with the blood-vessels, practically fills it, is incompressible.

Any increase or decrease in the amount of blood supplying the brain is brought about entirely by variations in the *velocity* with which the blood flows through the cerebral vessels. It has already been pointed out that if the width of the bed through which the blood is flowing remains constant, the velocity of the flow will vary directly with the pressure which tends to drive the blood along the vessels. In the body this pressure is the general arterial pressure, and since the volume of the cerebral vessels remains constant, the velocity of the flow of blood through them will depend entirely on the arterial pressure, provided there is no obstruction to the escape of blood from the cerebral veins. If the arterial pressure rises, the arteries become rather more distended and occupy more space, and as the total volume of the cerebral vessels remains unaltered, the expansion of the arterioles must be accompanied by narrowing of the capillaries and veins. The narrowing is not sufficient to cause any obstruction to the escape of blood through these vessels, and the amount of blood flowing through the brain is greatly increased. If the general arterial pressure falls, the velocity of the blood flow through the brain diminishes, and the amount of oxygen reaching it in a given time is correspondingly decreased. When the supply of oxygen falls, the vaso-motor centre is stimulated, causing general vaso-motor constriction, and thereby raising the blood pressure to such a level that the flow of blood through the brain is again sufficient to provide an adequate supply of oxygen. Thus the blood supply to the brain is determined almost entirely by conditions outside the brain itself, being increased whenever the abdominal vessels are constricted and diminished when these dilate. The brain is protected from lack of oxygen by the vaso-motor centre in the manner just described.

If the blood supply to the brain becomes inadequate, the respiratory centre is also stimulated, and the increased respiratory movements bring more blood to the heart, and so enable it to expel more blood at

each beat, and thus to assist the vaso-motor centre in raising the blood pressure.

The pressure of the contents upon the wall of the skull is equal to that within the capillaries of the brain. It cannot be greater than the capillary pressure, since in these circumstances the capillaries would collapse and the flow of blood through the brain would cease. The intra-cranial pressure can be raised by any obstruction to the escape of blood from the cerebral veins, or by the presence within the skull of a foreign body, such as a blood clot. In the latter case the pressure within the skull may rise sufficiently to compress the capillaries or even actually to obliterate them. Such compression, which inevitably diminishes the blood supply to the brain, may cause loss of consciousness and other serious symptoms.

SUMMARY OF THE ESSENTIAL FEATURES OF THE CIRCULATION.

The most important functions of the circulatory mechanism are (1) to maintain a continuous slow stream of blood through the capillaries so as to provide the most favourable conditions for the passage of oxygen and nutritive material from the blood to the tissues and of waste products into the blood; and (2) to keep the arterial pressure at such a height as to ensure an adequate supply of blood to all parts of the body. The carrying out of these functions in response to the varying needs of the tissues and to stimuli reaching the body from the outer world is chiefly effected through the nervous system, which controls the rate of the heart and the calibre of the arterioles. In the attainment of this end, the heart and arterioles are made to co-operate with each other. For instance, if the peripheral resistance becomes very great, the rise in blood pressure stimulates the vagus centre, the heart beats more slowly, and the pressure falls to its normal level (Marey's law). Again, if the heart is beating against a high peripheral resistance, its work is lightened by impulses passing along the depressor nerve, which reflexly diminish this resistance. If the blood pressure falls, it is restored to the normal level by increased activity of the vaso-motor centre, which is assisted in many cases by an increased output of blood from the heart.

These regulative mechanisms depend for their efficiency upon the nutrition of the heart itself, and upon the maintenance of its normal rhythm. Broadly speaking, the rate of the heart is determined by the influence of the nervous system, and the force of the beat by the state of nutrition of its muscular fibres. The latter depends almost entirely upon the amount and character of the blood supplied to the heart by the coronary vessels; if its nutrition is impaired the heart beats

more and more feebly, fails to expel its contents into the aorta, and finally the circulation may come to a standstill. Thus the nutrition of the heart muscle is ultimately the most important feature of the circulatory mechanism.

SECTION VI.

THE FORMATION OF LYMPH.

Except in the spleen, and possibly the liver, the blood does not come into direct contact with the cells of the tissues. It is separated from them not only by the walls of the capillaries, but by a fluid called lymph or tissue fluid, which lies between the capillaries and the tissue cells themselves. From these spaces the lymph passes into narrow channels (lymphatic vessels) lined by endothelial cells. These channels unite and finally end in a single vessel, the thoracic duct, which opens into the junction of the left jugular and subclavian veins, and conveys the lymph from the greater part of the body into the blood stream. The lymph from the right side of the head and neck, and the right fore-limb passes into a vessel which opens into the junction of the right jugular and subclavian veins. The lymph has been described by Foster as a "middle man," since, on the one hand, it receives from the blood oxygen and dissolved nutrient materials and passes them on to the tissue cells, and, on the other hand, it receives from the tissue cells carbonic acid and other waste products and returns them to the blood stream. The interchange of material between the blood and the tissues takes place by diffusion (p. 14), and in this way the tissues are nourished without any increase necessarily taking place in the amount of tissue fluid.

THE COMPOSITION OF LYMPH.

Lymph can be collected by placing a cannula in the thoracic duct of an animal, such as a dog or horse. If the animal has not been recently fed, the lymph is a clear, colourless fluid having a specific gravity of about 1015, and usually clots when allowed to stand. It contains some lymphocytes, 4 to 5 per cent. of protein, the proteins being the same as those in blood serum, and also various salts and extractives. After a meal the lymph is milky in appearance, owing to the presence of large numbers of minute fat globules. The fat is derived from that taken in the food, which, after absorption from the digestive tract, passes into the intestinal lymphatic vessels (lacteals). In their course the vessels pass through the lymphatic glands, in which lymphocytes are formed; these enter the lymph stream and are carried into the blood.

THE FORMATION OF LYMPH.

Although the exchange of material between the blood and the tissues does not necessarily increase the amount of lymph in the tissue spaces, it is found that, in point of fact, lymph is constantly being formed in the body, and, after passing along the lymphatic vessels, is returned to the blood stream along the thoracic duct. The formation of lymph has been attributed by some writers to secretion by the walls of the capillaries, and by others to the action of purely physical processes such as filtration and osmosis. If the latter view is correct, a rise in capillary pressure should lead to an increase in the formation of lymph; and this is found to be the case.

The pressure in the capillaries is much more easily altered by a rise in the venous pressure than by a rise in the mean arterial pressure; a rise in venous pressure, by obstructing the escape of blood from the capillaries, at once raises the capillary pressure. Hence a large rise in capillary pressure can be produced by ligaturing the vena cava or portal vein; and this is followed by a great increase in the flow of lymph from the thoracic duct.

Again, when a large quantity of saline solution is injected into the circulation, the blood is not only increased in amount, but becomes more watery, the condition being called *hydræmic plethora*. The arterial pressure remains almost unaltered, but the veins are distended to contain the greater part of the fluid thus added to the circulation, and the venous pressure rises; as a result the pressure in the capillaries also rises, and the flow of lymph from the thoracic duct becomes very rapid.

Hydræmic plethora may also be produced by injecting into the blood a strong solution of dextrose or other crystalloid body; this raises the osmotic pressure of the blood, and water passes by osmosis from the tissues into the blood, thereby increasing its volume and raising the capillary pressure. In these circumstances a great increase takes place in the flow of lymph from the thoracic duct, as is seen in the following table:—

HYDRÆMIC PLETHORA.

Periods of Ten Minutes.	Arterial Blood Pressure.	Pressure in Inferior Vena Cava.	Flow of Lymph.
1	100 mm. Hg	12 mm. water	3·0 c.c.
40 grm. dextrose dissolved in 50 c.c. water injected into a vein.			
2	105 mm. Hg	180 mm. water	33·0 c.c.
3	120 ,, ,,	50 ,, ,,	31·0 ,,
4	118 ,, ,,	25 ,, ,,	20·0 ,,

From these experiments it may be concluded that the walls of the capillaries form a membrane through which lymph can be filtered off, and that the amount of fluid which passes through the membrane in a given time depends directly upon the capillary pressure.

Another factor in the formation of lymph is the variable readiness with which filtration takes place through the capillaries in different parts of the body under the same pressure. The least permeable capillaries are those of the limbs, the most permeable being those of the liver; and almost all the lymph flowing from the thoracic duct of a resting animal is formed in the liver and digestive tract. The permeability of the capillaries can be increased by the injection of various substances called *lymphagogues*, including peptone and leech extract. The injection of one or other of these substances into the blood stream leads to an increased formation of lymph, although the capillary pressure, after a short time, is almost unaltered. The lymph is derived almost entirely from the liver, the capillaries of which become more permeable, as is shown by the fact that, if the lymphatic vessels of the liver are ligatured, the subsequent injection of peptone does not increase the formation of lymph.

The permeability of the capillaries is also increased when their nutrition is impaired, *e.g.* by lack of oxygen, and this may give rise to dropsy.

The formation of lymph is also dependent upon the metabolism of the tissues themselves. The injection into the blood of bile salts, for example, leads to the secretion of bile by the liver, and the flow of lymph from the thoracic duct is increased. This is not due to raised capillary pressure or to changes in the permeability of the capillaries, but is brought about in the following manner. In normal circumstances the osmotic pressure of the tissue cells, the lymph, and the blood is almost the same. When the metabolism of the liver is increased, metabolic products are formed in the liver cells and diffuse into the lymph, raising the osmotic pressure of the lymph and liver cells as compared with that of the blood. Consequently water passes from the blood into the lymph, and this fluid is increased in amount and gives rise to a larger flow from the thoracic duct. Similar results have been observed in other organs, and probably increased functional activity of any tissue in the body leads to increased formation of lymph. We may conclude, therefore, that lymph formation is not a secretory process, but is brought about by purely physical processes, namely, filtration and osmosis; and the factors concerned in its production are (1) the capillary pressure, (2) the degree of permeability of the capillary walls, and (3) the metabolic activity of the tissues. There is no reason to suppose that in health the permeability of the

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capillaries alters, and therefore the formation of lymph is increased chiefly by variations in the first and third of these factors.

ABSORPTION FROM THE TISSUES.

If a saline solution containing some readily recognisable substance, such as potassium iodide, is injected under the skin or into the pleural or peritoneal cavity, it rapidly disappears, and the presence of potassium iodide can be demonstrated in the blood or urine some time before it appears in the lymph flowing from the thoracic duct. This experiment makes it clear, first, that water and substances in solution can be readily absorbed, and, secondly, that the absorption does not take place into the lymphatic vessels, but through the capillary walls directly into the blood. Similarly, tissue fluid may be absorbed through the capillary walls; after hæmorrhage, for instance, the volume of the blood is rapidly brought back to the normal by the passage of fluid from the tissue spaces into the blood. This process depends upon the fact that proteins exert an osmotic pressure, which, though very small in comparison with that of a solution of crystalloid bodies, is yet appreciable. The osmotic pressure of the crystalloids in blood and lymph is much the same, but, owing to the percentage of protein in blood being higher than that in lymph, the blood has a slightly higher osmotic pressure, and fluid tends to pass from the lymph into the blood. At the same time, fluid is being filtered through the capillary wall from the blood into the lymph at a rate varying with the capillary pressure. These two processes, namely, filtration and absorption, tend to balance one another and to keep the amount of tissue fluid constant. The balance may be disturbed either by a rise or by a fall of capillary pressure. In the former case, the amount of tissue fluid is increased, whereas, if the capillary pressure falls, for instance after severe hæmorrhage, the amount of fluid absorbed exceeds that which is filtered through the capillary walls; and the volume of the blood increases at the expense of the lymph and tissues.

The absorption of saline solution, placed under the skin, is brought about partly by simple diffusion of the dissolved substances into the blood, and partly by the osmotic pressure exerted by the proteins in the blood.

THE FLOW OF LYMPH.

The tissue fluid is formed under a pressure which is probably rather less than that in the capillaries, and this pressure tends to drive the lymph towards the thoracic duct; the pressure in the duct where it

opens into the great veins is at most 2 to 3 mm. Hg, and may be negative. Other and more important factors are muscular and respiratory movements. Every muscular movement, by compressing the lymphatic vessels, forces the lymph on towards the thoracic duct. With each inspiration, the abdominal pressure rises and the intestinal lymphatic vessels are compressed; at the same time, the pressure on the thoracic duct becomes negative, and lymph is sucked into the chest. The effect of these movements is assisted by the presence of valves in the larger lymphatic vessels, which prevent any backward flow of lymph.

CHAPTER IX.

THE RESPIRATORY SYSTEM.

SECTION I.

Respiration consists in the transference of oxygen from the atmospheric air to the tissues of the body, and of carbonic acid from the tissues to the outer air. In man and most vertebrates, the oxygen and carbonic acid are carried to and from the tissues respectively by the blood, which, on the one hand, receives oxygen in the lungs and gives it up to the tissues, and, on the other hand, receives carbonic acid from the tissues and gives it up in the lungs. In fishes and many invertebrates, the lungs are replaced by gills. The transference of oxygen from the atmosphere into the blood and of carbonic acid from the blood into the atmosphere is called *external* respiration, the interchange of gases between the blood and the tissues being termed *internal or tissue* respiration.

THE STRUCTURE OF THE AIR PASSAGES AND LUNGS.

The respiratory system consists of the lungs and the air passages leading to them, namely the mouth and lower half of the nasal cavity, the upper part of the pharynx, the larynx, trachea, and bronchi. The trachea is a wide tube about 4½ inches in length in man, and is lined by stratified epithelium, the inner layer being ciliated. The epithelium rests upon a thick basement membrane, beneath which is a layer of elastic fibres running longitudinally; external to this membrane is areolar tissue in which lie many small glands, which secrete mucin. The trachea is strengthened by C-shaped hoops of cartilage, and on its posterior wall is a layer of unstriped muscle, the fibres of which run transversely. The cartilaginous rings keep the lumen of the trachea patent, and prevent its occlusion by external pressure. The fluid formed by the small mucous glands moistens the inner surface of the trachea, and serves also to catch bacteria or particles of dust, which

are carried in with the inspired air; the cilia, by their movement, carry the fluid up the trachea into the pharynx.

The main bronchi are similar in structure to the trachea.

In the lungs the bronchi branch in a tree-like manner, the final ramifications opening into the pulmonary air cells. The larger intrapulmonary bronchi are lined by columnar ciliated epithelium resting on a basement membrane. Lying under this basement membrane are longitudinally disposed elastic fibres with loose connective tissue. More externally is a layer of smooth muscle fibres arranged circularly, the

FIG. 94.—Section of lung of cat, showing termination of bronchus. (From Gray's *Anatomy.*)

bronchial muscle. External to the bronchial muscle is a fibrous coat containing scattered, irregular plates of hyaline cartilage.

The smaller bronchi (bronchioles) have no cartilaginous plates, but their muscular coat is well marked.

Each bronchiole leads into a small number (three or four) of wider thin-walled spaces, lined by flattened epithelium, and called *atria.* Out of each atrium open two or three blind diverticula, each of which is called an *infundibulum.* The walls of the infundibula are studded with hemispherical sacs known as *alveoli,* which are lined by flattened, non-nucleated, epithelial cells. Between adjacent alveoli there is a dense network of capillaries, supported by a small amount of fine connective

and elastic tissue; the network of capillaries is thus common to the two adjacent air cells, and the blood in the capillaries is separated from the air in the alveoli merely by two thin layers of epithelium. In birds, even the alveolar epithelium appears to be absent, the blood and air being separated solely by the capillary wall.

The branches of the pulmonary artery accompany the bronchi, and open into the alveolar capillary network, from which blood is carried back to the left auricle by the pulmonary veins. Oxygenated blood is supplied to the bronchi by the bronchial arteries.

The lungs nearly fill the thoracic cavity, the space between them being occupied by the heart, great vessels, and other structures. Each lung is covered by a thin membrane, consisting of a superficial layer of flattened epithelium resting on connective tissue; the membrane is known as the pleura, and is reflected at the root of the lung on to the chest wall. Each pleura thus forms a closed sac, the walls of which are normally in apposition; their inner surfaces are moistened by a small amount of fluid, resembling lymph, and glide over one another with every movement of the chest wall and lung.

THE RESPIRATORY MOVEMENTS.

The thorax is a completely closed box which alters in shape and size with each respiratory movement; with inspiration it becomes larger in all its diameters, vertical, antero-posterior, and transverse, returning to its former size during expiration. This increase in size is brought about partly by the upward movement of the ribs, partly by the descent of the diaphragm.

The diaphragm consists of a muscular sheet with a tendinous central portion. In the position of rest it forms a dome projecting towards the thoracic cavity, and when it contracts the summit of the dome, namely the tendinous portion, is drawn downwards from 1 to 2 cm., thus increasing the vertical diameter of the chest. The extent to which the central tendon can be drawn downwards is limited by the resistance of the abdominal viscera, and when the limit is reached, the direction of the pull of the costo-sternal muscle fibres of the diaphragm is reversed so that the lower end of the sternum and the movable ribs are raised. The spinal fibres of the diaphragm, the lower attachment of which is a fixed point, still exert a downward pull upon the central tendon.

The Ribs.—At the beginning of inspiration the first pair of ribs and the manubrium sterni are fixed by the resistance of the cervical structures, and the second to the fifth pairs of ribs are drawn upwards by the contraction of the external intercostal muscles and the serratus

posticus (posterior) superior. Since the ribs slant downwards and forwards from their vertebral articulation, this upward movement carries forward the sternum and increases the antero-posterior diameter of the chest. At the same time the ribs rotate slightly round the axis represented by a line drawn from their vertebral to their costal attachments, and their lower borders, which in the expiratory position are inverted, become everted. The costo-chondral angle is also opened out. By these means the transverse diameter of the chest is enlarged.

The lower ribs are raised partly by the external intercostal muscles, partly also by the contraction of the diaphragm, and partly by the interchondral portion of the internal intercostal muscles.

Thus the muscles concerned in quiet inspiration are the diaphragm, the external intercostal muscles, the interchondral portion of the internal intercostal muscles, and the serratus posticus (posterior) superior. The entrance of air into the lungs is also assisted by widening of the glottis, and, if the breathing is at all laboured, by dilatation of the alæ nasi. In forced inspiration, other muscles such as the trapezius, pectoral muscles, sterno-mastoid, and rhomboids are called into play.

During quiet expiration, the chest returns to its former shape and size, mainly on account of the elasticity of the chest wall and lungs, and of the abdominal wall and abdominal contents; the downward movement of the ribs during expiration is also assisted by the contraction of the costal part of the internal intercostal muscles, which pass downwards and backwards from each rib to the one immediately below it. In forced expiration the accessory muscles employed are mainly those of the abdominal wall.

Quiet respiration in men is carried out principally by the movements of the diaphragm. In women the larger part is played by the movements of the upper ribs, chiefly on account of wearing of tight clothing, which interferes with the movement of the diaphragm and lower ribs.

THE EFFECT OF THE RESPIRATORY MOVEMENTS ON THE LUNGS.

The passage of air into and out of the lungs during respiration is brought about by purely mechanical causes, which can be roughly illustrated by the aid of an artificial model. A thin-walled rubber bag is placed in a glass vessel closed by a cork; the bag is attached to a glass tube, which passes through the cork and is open at the top. The bottle is connected by another tube with a mercury manometer and by a third tube with a suction pump, by means of which air can be sucked out of it.

At the outset of the experiment the air in the bottle is at the same pressure as that of the atmosphere, and the bag is collapsed. If a little air is sucked out of the bottle, the pressure falls, and, since the pressure within the rubber bag remains unaltered, a difference of pressure is set up on its inner and outer surfaces. The bag expands, air being sucked into it along the glass tube to fill the extra space thus provided, until the pressure within it and outside it becomes nearly equal; but the pressure outside the bag is finally a little less than atmospheric pressure, because a part of the pressure in the bag is used up in overcoming the tendency of its stretched elastic wall to collapse. When more air is sucked out of the bottle the rubber bag expands still further, but the pressure in the bottle remains negative, that is, less than atmospheric pressure. When the bottle is opened, the pressure on each side of the bag becomes the same, and it collapses.

In the body the lungs take the place of the bag, the bottle is represented by the chest, and the changes in the pressure on the outer surface of the lungs are brought about by alteration in the size of the chest cavity. If a small tube, connected with a manometer, is passed through the chest wall of an animal into the pleural cavity, the pressure within the chest is seen to be lower than that of the atmosphere; at the end of expiration the difference is usually about 6 mm. Hg. When the chest enlarges during inspiration, the pressure on the outer surface of the lungs diminishes, and, as the pressure within them remains unchanged, they expand still further. Owing to the greater force required to bring about this additional expansion of the lungs, the pressure in the pleural cavity is further diminished, and amounts on an average to 730 mm. Hg. The negative pressure in the pleural cavity thus varies from – 6 mm. Hg during expiration to – 30 mm. Hg or more during inspiration, and represents the pressure required to overcome the tendency of the expanded lungs to collapse by virtue of their elasticity. When the lungs expand further during inspiration, air rushes in to fill the additional space; during expiration air is expelled. The expansion of the lungs during inspiration is due almost entirely to the enlargement of the infundibula and atria, and the portions of the lungs which expand most are those in contact with the diaphragm and ribs; the dorsal and mediastinal surfaces and the apex are much less expansile.

If the chest is opened, either during life or after death, the pressure on both the outer and the inner surfaces of the lungs is that of the atmosphere, and owing to their elasticity the lungs collapse. In the condition known as emphysema, the elastic tissue of the lungs atrophies

and they do not collapse when the chest is opened. In the new-born infant, the lungs, even in their collapsed condition, fill the chest. As the child grows, the capacity of the chest increases more rapidly than does the size of the lungs; and the lungs of the adult are considerably expanded even at the end of expiration.

Since with each expansion of the chest the lungs increase in size so as to fill completely the extra space thus provided, the amount of air entering the lungs at each breath varies with the extent of the respiratory movement. In quiet respiration it amounts to 350–500 c.c., and is spoken of as *tidal* air. The additional volume of air, which can be taken into the lungs by forced inspiration, amounts on an average to about 1500 c.c. and is called *complemental* air. The largest amount of air which can be expelled from the lungs by the most violent expiration, made at the end of an ordinary breath, is termed *supplemental* air; it varies in different individuals from 1000 to 1500 c.c. Even after the most forcible expiration, a considerable amount of air—usually about 1000 c.c. —still remains in the lungs, and is spoken of as *residual* air. The total volume of air which can be taken into and expelled from the lungs by the most forcible inspiration and expiration, namely, the sum of the tidal, complemental, and supplemental air, is termed the *vital capacity* of the chest, and is from 3000 to 3500 c.c. These figures are obtained by allowing the individual to breathe into a spirometer, which is a small gasometer provided with a graduated scale. When the subject breathes into or out of the spirometer, the air chamber rises or falls, the increase or decrease of its contents, thus produced, being read off on the scale.

Tidal air 500 c.c. . . .	Vital capacity 3500 c.c.
Complemental air 1500 c.c. .	
Supplemental air 1500 c.c. .	
Residual air 1000 c.c.	

The normal rate of respiration in adults is 15 to 18 a minute. Expiration follows inspiration immediately, and is succeeded by a slight pause before the next inspiration begins. Children breathe more rapidly, the rate in the infant being about 40 a minute.

Ordinary quiet breathing is usually called *eupnœa*, and an increase in the depth of the respiratory movements is called *hyperpnœa*; if these movements are not only deeper, but also laboured, the term *dyspnœa* is applied to them. A temporary cessation of breathing is known as *apnœa*.

If the ear is placed in contact with the chest wall, a faint sound—the vesicular murmur—is heard during inspiration; it is believed to be

produced by the passage of air through the larger respiratory passages, the sound being modified in its conduction through the substance of the lung. On listening over the trachea and large bronchi, the sound is louder and is audible both during inspiration and expiration. The character of the sound is altered in disease of the lungs or pleura.

SECTION II.

THE CHEMISTRY OF RESPIRATION.

The composition of expired air differs considerably from that of the atmosphere, the average difference being as follows:—

	Nitrogen.	Oxygen.	Carbonic Acid.
Inspired air . .	79	20·96	0·04
Expired air . .	79·4	16·50	4·1
		4·46	4·06

The increased percentage of carbonic acid in expired, as compared with inspired, air is 4·06, the difference between the percentage of oxygen in inspired and expired air being 4·46, so that the total volume of the air expired is less than that inspired. It is for this reason that the relative amount of nitrogen in expired air is slightly increased. The ratio of the amount of carbonic acid leaving the body to the amount of oxygen taken into the body and not reappearing in expired air, is known as the respiratory quotient, and is usually expressed as $\frac{CO_2}{O_2}$. In the table it is $\frac{4·06}{4·46} = 0·90$. Its significance will be discussed subsequently (p. 343).

In addition to containing less oxygen and more carbonic acid, the expired air is fully saturated with water, and is at the body temperature. It has been stated that small quantities of poisonous substances are also present in expired air, and that the accumulation of these substances in crowded and ill-ventilated rooms is the cause of the headache and other uncomfortable symptoms experienced in these circumstances. Careful experiments have shown that this is not the case, and that the symptoms are due partly to the accumulation of carbonic acid in the air, and make their appearance when this reaches 0·1 per cent. or more, and partly, as Leonard Hill suggests, to a high temperature and lack of

currents of air in the room. They may be avoided by constant renewal of the air in rooms by adequate ventilation.

The expired air comes partly from the lungs, partly also from the respiratory passages, namely the bronchi, trachea, pharynx, and nose. Since the air in these passages undergoes very little change in composition during respiration, they are known as the "dead space," the capacity of which varies from 130 to 150 c.c. and is very constant for the same individual. The air contained in the dead space is expelled during the first part of expiration, the air expelled during the latter part of expiration, particularly if this is forcible, coming directly from the alveoli of the lungs. Since the interchange of oxygen and carbonic acid between the blood and the air in the lungs takes place solely in the alveoli, it is of great importance to ascertain the composition of the alveolar air.

Haldane has devised a simple apparatus for collecting samples of alveolar air in man. It consists of a piece of rubber tubing about 1 inch in diameter, 3 or 4 feet long, and provided with a mouthpiece. About 2 inches from the mouthpiece the tube is connected with a sampling tube (fig. 95), which has previously been made vacuous.

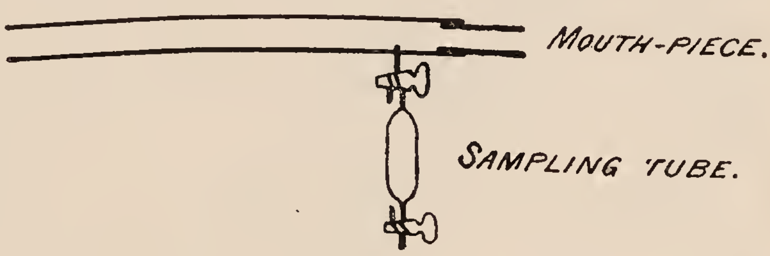


FIG. 95.

The subject breathes normally for a few moments, and then, at the end of a normal inspiration, he expires deeply through the mouthpiece and instantly closes it with his tongue. The upper tap of the receiver is at once opened, and air rushes into it from the tube; the tap is then closed, and the sample can be analysed. A second similar experiment is made, in which the subject expires deeply at the end of a normal expiration, and another sample of air is obtained. The mean of the analyses of the two samples gives the average composition of the alveolar air.

The reason for taking two samples is that at the end of inspiration the lungs contain a maximum percentage of oxygen, whereas at the end of expiration they contain a maximum percentage of carbonic acid. The amount of carbonic acid in alveolar air obtained by this method varies from 5 to 6 per cent. in different individuals, but is remarkably constant in the same individual; the amount of oxygen is usually 13 to 14 per cent. Alveolar air thus contains considerably less oxygen and more carbonic acid than ordinary expired air, the reason being that, in the expired air, the alveolar air is mixed with the contents of the

dead space, the composition of which differs but little from that of the atmosphere.

The air is analysed by shaking up a known volume with caustic potash, which absorbs the carbonic acid ; the diminution in volume represents the amount of carbonic acid present in the air. The air is then shaken up with pyrogallic acid, which absorbs oxygen, and the diminution in volume is again measured. The residual gas is regarded as being nitrogen.

THE GASES IN THE BLOOD.

Before discussing the means by which the interchange of oxygen and carbonic acid between the blood and air in the lungs is effected, it is necessary to determine, first, the amount of these gases in the blood, and, secondly, the conditions in which they are held in it.

If blood is exposed to a vacuum, there is a considerable evolution of gas, which may be collected and analysed. For this purpose, some form of gas pump is usually employed, the composition of the gas being subsequently ascertained by exposing it first to potash, which absorbs carbonic acid, and secondly to pyrogallic acid, which absorbs oxygen. By this means it is found that 100 volumes of blood give off about 60 volumes of gas, the composition of which varies according to whether the blood is arterial or venous. The total quantity of oxygen which 100 volumes of blood can take up or give off is called its *oxygen capacity.*

GASES IN THE BLOOD (DOG).

	Oxygen.	Carbonic Acid.	Nitrogen.
100 volumes of Arterial blood yield . .	20 vols.	40 vols.	1–2 vols.
100 volumes of Venous blood yield . .	8–12 ,,	46–48 ,,	1–2 ,,

This method necessitates the use of comparatively large quantities of blood (10 to 20 c.c.) in order to give accurate results ; and Barcroft has devised an apparatus, by means of which the estimation of the blood gases can be carried out with very small quantities (1 c.c. or even 0·1 c.c.) of blood. The method has the advantage of being readily applicable to man, and depends upon the fact that, when potassium ferricyanide and a trace of alkali (usually ammonia) are added to blood, all the oxygen previously in combination with hæmoglobin is evolved, and the amount of oxygen given off from a known volume of blood can

be measured. The hæmoglobin then takes up an equivalent amount of oxygen from the reagents, being converted into methæmoglobin. The probable course of the reaction is represented by the equation

$$\underset{\text{Oxyhæmoglobin}}{HbO_2} + 4K_3Fe(CN)_6 + 4KOH = \underset{\text{Methæmoglobin}}{HbO_2} + 4K_4Fe(CN)_6 + 2H_2O + O_2.$$

Barcroft's differential apparatus consists of a manometer, of which the bore is 1 mm., and which is provided with a scale graduated in millimetres. Attached to each limb is a small bottle, which is detachable, and by means of taps each bottle can be connected with or shut off from the outer air. The manometer is partially filled with clove oil.

(1) To determine the *oxygen capacity* of a sample of blood, 2 c.c. of dilute ammonia and 1 c.c. of the blood to be examined are placed in each bottle, and the bottles are shaken so that the blood is thoroughly laked and saturated with oxygen. The stoppers are carefully greased, and 0·2 c.c. of a saturated solution of potassium ferricyanide is placed in the reservoir in the stopper of one bottle A. The bottles are then attached to the manometer and placed in a water bath, the taps being open. When the reading of the manometer becomes constant, the taps are closed, thereby excluding the bottles and the manometer from the outer air, and the apparatus is tilted so that the ferricyanide runs into the blood in A, which gives off its oxygen. The level of the clove oil falls in the limb attached to the bottle A and rises in the opposite limb, and the bottles are replaced in the water bath until the readings become constant. If the difference of level on the two sides is 60 mm., this difference, multiplied by the constant of the apparatus (which may be taken as 3·0), represents the amount of oxygen given off by the blood; thus 60 mm. × 3·0 = 180 c.mm. oxygen. Since 1 c.c. of blood gives off 0·18 c.c. of oxygen, 100 c.c. of blood will give off 18·0 c.c. oxygen, and this is its oxygen capacity. We have taken 3·0 as the constant of the apparatus, but it must be remembered that each apparatus has its own constant, which may be slightly greater or less than 3·0.

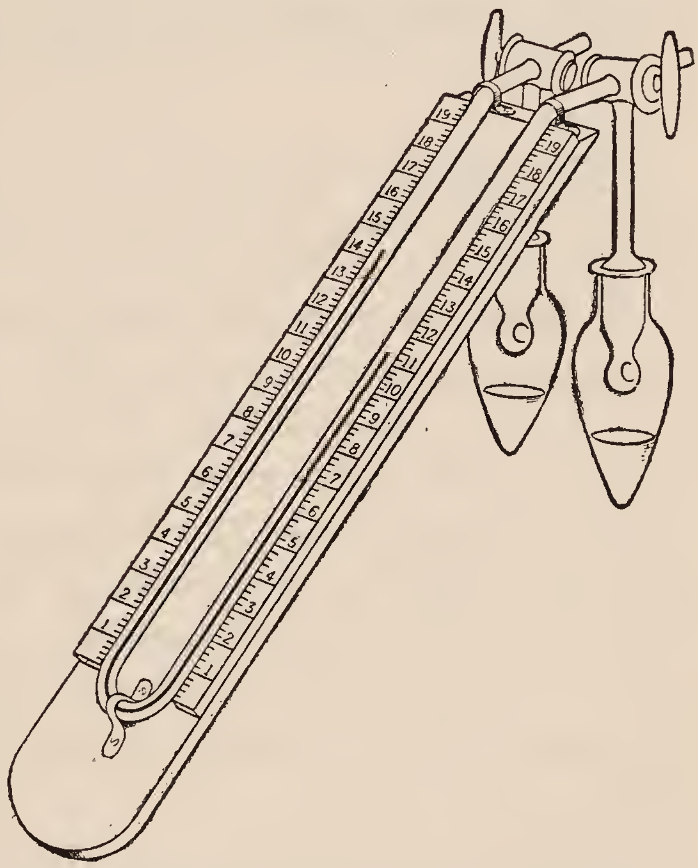


FIG. 96.—Barcroft's blood-gas apparatus. (From Barcroft, *Respiratory Function of the Blood.*)

(2) To determine the *amount* of oxygen present in a given sample of blood, 2 c.c. of dilute ammonia are placed in each bottle; 1 c.c. of the blood to be examined is carefully placed under the ammonia at the bottom of one bottle A, and thus kept from contact with the air. 1 c.c. of fully oxygenated (saturated) blood is placed in the other bottle B. The stoppers are greased, the bottles are attached to the manometer and placed in a water bath, the taps being open. When the reading of the manometer becomes constant, the taps are closed and the apparatus is shaken in order to lake the blood in each bottle. The blood in bottle B, being already fully saturated, takes up no more oxygen when brought into contact with the air in the bottle. If the blood in the bottle A is already fully saturated with oxygen, it takes up no more oxygen, and the

reading of the manometer remains unchanged ; but if it is not fully saturated, it takes up some oxygen, and the level of the clove oil rises in that limb of the manometer. The manometer is replaced in the water bath till the reading is constant. If the difference in the level of oil in the two limbs is 20 mm., the blood must have taken up 20 mm. $\times$ 3·0 = 60 c.mm. of oxygen ; and if its total oxygen capacity is ascertained, the degree to which it was previously saturated can be calculated.

Thus, if the oxygen capacity of 1 c.c. blood was 0·18 c.c., and it took up in the foregoing experiment 0·06 c.c. oxygen, it must have previously contained 0·12 c.c., and its percentage saturation was $100 \times \frac{0 \cdot 12}{0 \cdot 18} = 66$ per cent.

THE CONDITION IN WHICH THE GASES ARE HELD IN THE BLOOD.

Theoretically, the gases in the blood might be either simply dissolved in it or chemically combined with some constituent of the blood. In order to decide which of these possibilities is the correct one, it is necessary to consider first the conditions which modify the amount of any gas present in a fluid such as water. On exposing water to the air, a certain amount of oxygen and nitrogen is dissolved in it. Confining our attention to oxygen, the amount dissolved in a known volume of water depends upon (1) the pressure exerted by the oxygen upon the surface of the water, (2) the temperature of the water, and (3) the capacity of water to dissolve oxygen. The capacity of water to dissolve any gas is constant for the same gas, provided the pressure of the gas and the temperature of the water remain unchanged. Some gases, such as carbonic acid, are very soluble in water, others such as oxygen and nitrogen are only slightly soluble. The *coefficient of solubility* of a gas is defined as the amount of that gas which is dissolved at a given temperature in 1 c.c. of the liquid, when the pressure of the gas on the liquid is 760 mm. Hg.

Since the capacity of water to dissolve any gas is constant, the amount of the gas dissolved at a given temperature (which will be assumed to be constant) varies directly with the pressure of the gas on the surface of the liquid. When water is exposed to pure oxygen at atmospheric pressure, the pressure of oxygen on the water is 760 mm. Hg ; if it is exposed to atmospheric air, both the oxygen and nitrogen exert a pressure, which is proportional to their percentage in the air. In such a mixture of gases, the proportion of the total pressure exerted by the oxygen on the walls of the vessel containing it, or on the surface of a fluid, is called the *partial pressure* or *tension* of oxygen, and it is measured by determining (1) the percentage of oxygen in the gaseous mixture, and (2) the total pressure of the mixture. The partial pressure

of oxygen in atmospheric air is, therefore, 20 per cent. of 760 mm. Hg, namely 152 mm. Hg.

The Tension of Gas in a Fluid. — When water is exposed to a gaseous mixture containing oxygen, the molecules of oxygen tend to pass into the liquid and be dissolved; at the same time, the molecules of oxygen already in solution tend to pass from the water into the gaseous mixture. This tendency of the molecules of oxygen to leave the fluid is called the *tension* of oxygen in the fluid. When these two opposing processes are equal, the gaseous mixture and the fluid are in equilibrium, and the amount of oxygen dissolved in the fluid remains constant. In these circumstances, the tension of oxygen in the fluid is equal to the partial pressure of the oxygen in the gaseous mixture to which the fluid is exposed.

The tension of oxygen in a fluid cannot be measured directly, but is determined by placing samples of the fluid in a series of closed vessels, containing oxygen at various known partial pressures, and finding in which vessel the fluid neither gives off nor takes up oxygen. The tension of oxygen in the fluid in this vessel is equal to the partial pressure of the oxygen in the gaseous mixture to which the fluid is exposed; and if the amount of oxygen in the gaseous mixture is 5 per cent. and the total pressure of the gaseous mixture is 760 mm. Hg, the partial pressure of oxygen is 38 mm. Hg; this is equal to the tension of oxygen in the fluid. The forms of apparatus which have been devised for measuring the tension of a gas in a fluid are called *aërotonometers.*

The Tension of Oxygen in Blood.—In the case of water, oxygen is held in simple solution, and, if the temperature is constant, the amount of oxygen in the water varies directly with the partial pressure of oxygen in the air to which it is exposed. If the pressure of oxygen is doubled, twice as much is dissolved in the water. When similar experiments are carried out with blood, the amount of oxygen present in the blood, as determined by exposing it to a vacuum in a gas pump or by Barcroft's apparatus, is not proportional to the partial pressure of oxygen in the gaseous mixture to which the blood is exposed. For example, when the blood is in equilibrium with air containing oxygen at a partial pressure of 100 mm. Hg, it will contain about 18 volumes of oxygen per 100 volumes of blood. If the partial pressure of oxygen is reduced to 50 mm. Hg, the blood will contain 14·5 volumes of oxygen per 100 volumes of blood.

Since the amount of oxygen in blood is not *directly* proportional to the partial pressure of oxygen in the air to which the blood is exposed, it is evident that oxygen is not held in blood simply in solution. Further, a given volume of blood can take up many times as much

oxygen as an equal volume of water. Hence it is clear that oxygen must form an unstable compound with some constituent of the blood; this constituent is hæmoglobin, and a solution of pure hæmoglobin can take up from the air as much oxygen as blood containing the same amount of hæmoglobin. 1 gram of hæmoglobin can combine with approximately 1·34 c.c. oxygen, though this figure varies slightly in different animals, probably on account of slight differences in the character of the protein part of the hæmoglobin molecule.

If 100 c.c. of blood are exposed to an atmosphere of pure oxygen in a closed vessel at atmospheric pressure, they take up about 20 c.c. of oxygen. When the oxygen is slowly withdrawn from the vessel, so that the pressure on the surface of the blood gradually falls, the blood remains almost unaltered until the pressure falls to about 100 mm. Hg. With a further fall of pressure the blood rapidly gives off its oxygen, and, when the pressure falls to zero, all the oxygen has been evolved. Evidently the combination of hæmoglobin with oxygen is a reversible one; hæmoglobin gives off its oxygen when the pressure of oxygen is low, and takes it up when the pressure is high. This reversible action is usually indicated thus, $HbO_2 \rightleftarrows Hb + O_2$. It is to this power that hæmoglobin owes its value for respiration. In the alveoli of the lungs the partial pressure of oxygen is relatively high, and the blood becomes almost fully saturated with oxygen. The partial pressure of oxygen in the tissues is low, and, when the blood is carried round in the circulation to the tissues, the hæmoglobin dissociates, the oxygen set free being taken up by the tissues. The effect of a varying partial pressure of oxygen upon the combination between hæmoglobin and oxygen is shown in fig. 97. The curve shows the percentage of hæmoglobin present as oxyhæmoglobin with varying pressures of oxygen; when all the hæmoglobin is in the form of oxyhæmoglobin, it is said to be fully saturated. For pressures above 100 mm. Hg, the curve becomes almost a straight line.

This curve, which is known as the dissociation curve of hæmoglobin, is obtained in the following manner. A small quantity of blood is placed in an aërotonometer containing a mixture of oxygen and nitrogen at atmospheric pressure. A suitable form of tonometer is that shown in fig. 98; it consists of a glass cylinder, which can be rotated in water kept at a constant temperature. When the cylinder is rotated, the small amount of blood, previously placed in it, spreads out into a thin film over the inner wall of the cylinder, and after a short time the blood and gas come into equilibrium, and the blood neither takes up nor gives off oxygen. The cylinder is removed from the water bath, and the percentage of oxyhæmoglobin in the blood is estimated

by Barcroft's blood-gas apparatus. If, for example, the partial pressure of oxygen in the mixture of gases placed in the aërotonometer is 40 mm. Hg (corresponding with about 5 per cent. of oxygen), and

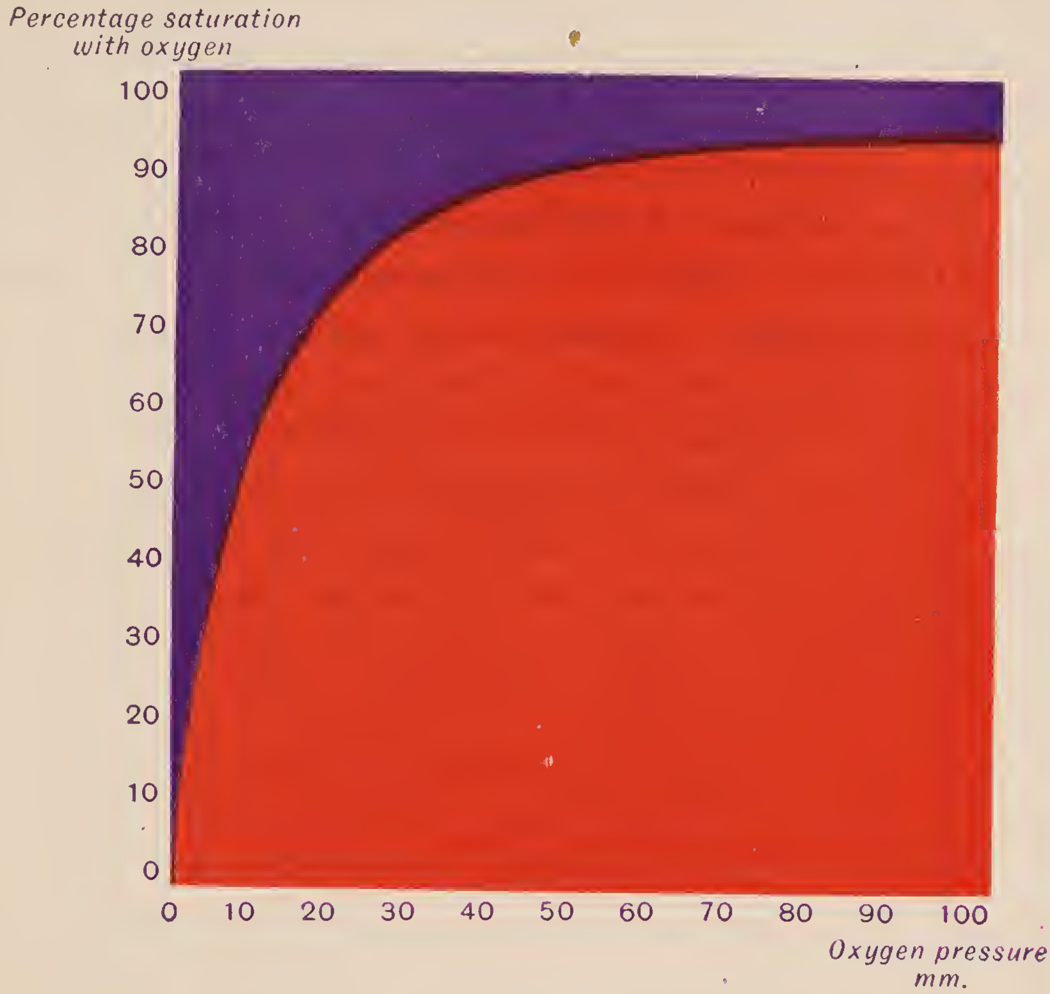


Fig. 97.—Dissociation curve of hæmoglobin dissolved in water at 37° C. (From Barcroft, *Respiratory Function of the Blood.*)

Oxyhæmoglobin is red, and reduced hæmoglobin is purple.

the percentage of oxyhæmoglobin in the blood, when in equilibrium with this mixture, is 70 per cent., that point can be marked on the chart. By making a series of such observations, and using varying percentages of oxygen in the gaseous mixture, a series of points is determined and plotted out. The line joining these points is the dissociation curve.

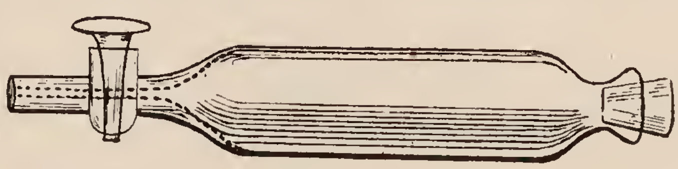


Fig. 98.—Barcroft's tonometer.

The form of the curve can be greatly altered by varying circumstances, and the dissociation curve of blood differs considerably from that of a solution of pure hæmoglobin, as may be seen in fig. 99. A comparison of the two curves shows that oxyhæmoglobin dissociates more readily in blood than when simply dissolved in water. When the partial pressure of oxygen is 20 mm. Hg, blood contains only 30 per cent. of its hæmoglobin in the form of oxyhæmoglobin, whereas in a watery solution of pure hæmoglobin 72 per cent. exists as

oxyhæmoglobin. This difference is chiefly due to the presence of salts, particularly potassium salts, in the blood, which render the combination between hæmoglobin and oxygen more unstable; when hæmoglobin is dissolved in water containing the same salts as those normally present in blood, its dissociation curve is identical with that of blood.

The other factors, which alter the form of the dissociation curve of blood, are (1) the temperature of the blood, and (2) the presence of carbonic or other acids. The higher the temperature of the blood and the greater the percentage of carbonic or other acids, the more

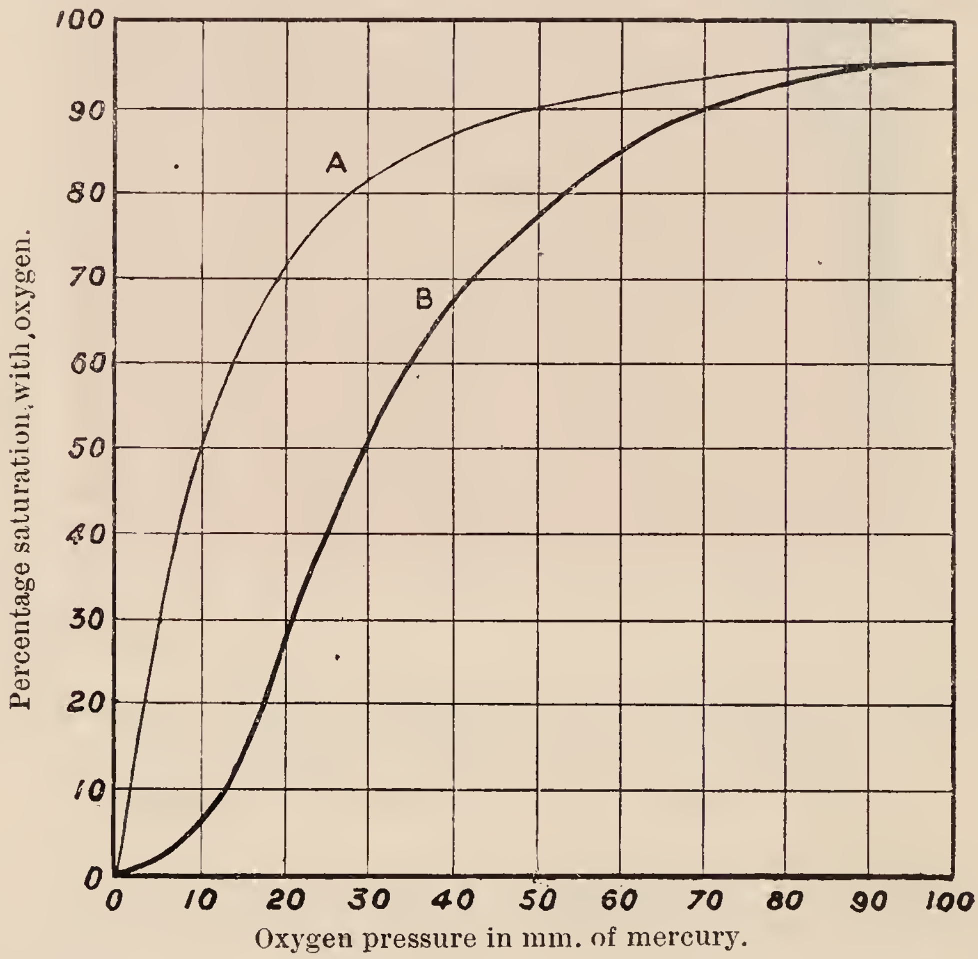


FIG. 99.—Dissociation curves (A) of hæmoglobin dissolved in water at 37° C., and (B) of blood at 37° C.

readily does the oxyhæmoglobin dissociate. The effect of carbonic acid and of lactic acid is shown in fig. 100. These factors not only modify the extent to which oxyhæmoglobin dissociates at the same partial pressure of oxygen, but also the *rate* at which it loses oxygen and becomes reduced; when an indifferent gas such as nitrogen is bubbled through a solution of blood, the blood becomes reduced much more rapidly if it contains an excess of carbonic acid or a small amount of lactic acid. The influence of carbonic or other acids on the readiness with which oxyhæmoglobin dissociates, when the pressure of oxygen to which it is exposed is low, is of great physiological importance. As the blood passes through the capillaries, it not only gives off oxygen, but also receives from the tissues carbonic acid and frequently

lactic acid. The greater ease with which the oxyhæmoglobin dissociates in these circumstances increases the supply of oxygen available for the tissues; and this effect will be especially marked and beneficial when the tissues are functionally active and are giving out large amounts of carbonic acid and require a larger supply of oxygen.

Although these conditions profoundly influence the rate of transference of oxygen from the blood to the tissues, they do not appreciably affect the amount of oxygen taken up by the blood as it passes through the lungs. The partial pressure of oxygen in the lungs is normally

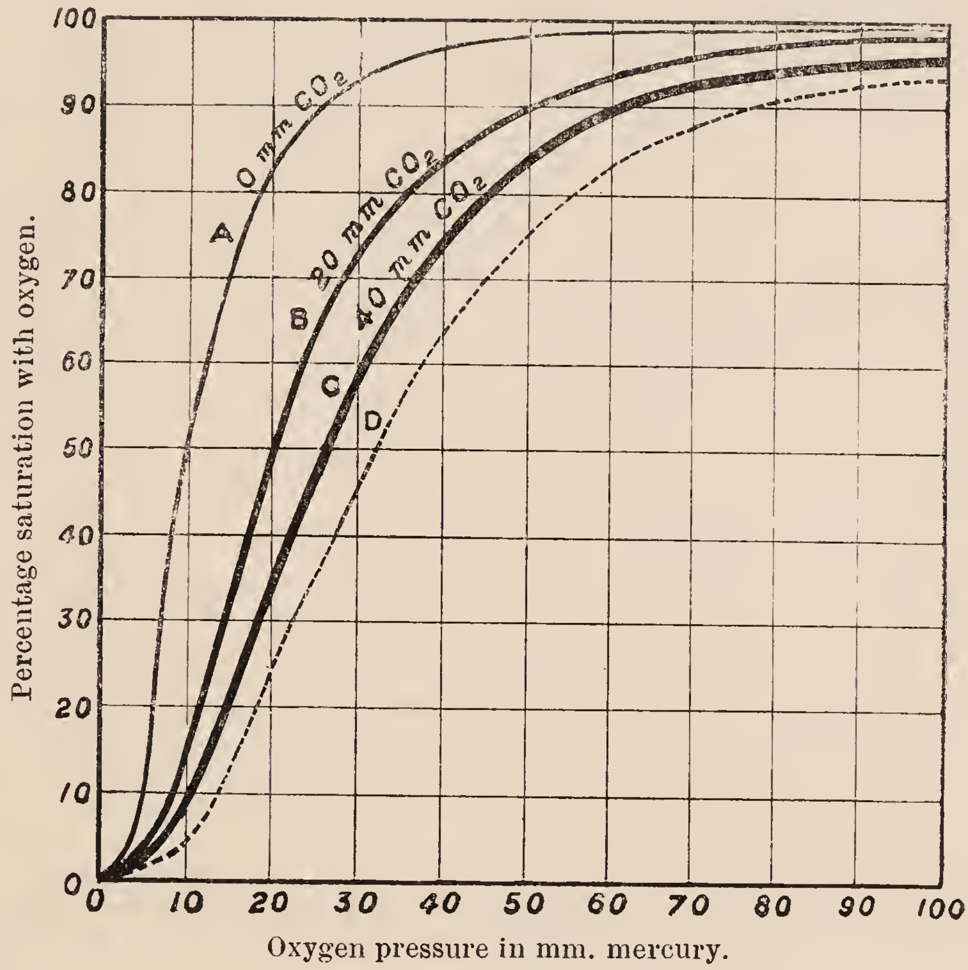


FIG. 100.—A, B, and C show the effect of varying tensions of CO_2 in blood on the dissociation curve of oxyhæmoglobin. The dotted line D is the dissociation curve of oxyhæmoglobin in blood to which 0·025 per cent. lactic acid was added.

just over 13 per cent. (about 105 mm. Hg), and a consideration of fig. 100 shows that at this pressure of oxygen the saturation of the blood will be practically the same, whether the blood is normal or whether it contains an excess of carbonic acid or a trace of lactic acid.

In addition to the oxygen thus combined with hæmoglobin, the blood contains oxygen in simple solution in the plasma, amounting at the body temperature to about 0·36 c.c. oxygen per 100 c.c. of blood.

Carbonic Acid in Blood.—The tension of carbonic acid in blood, when determined by means of an aërotonometer, is equal to a partial pressure of about 5 per cent. of carbonic acid. If the carbonic acid were simply dissolved in the blood, the latter would contain at this

tension only about $2\frac{1}{2}$ volumes of carbonic acid per 100 volumes of blood; but since 100 volumes of blood, when exposed to a vacuum, give off from 40 to 48 volumes of carbonic acid, the bulk of this must be in a state of chemical combination. It is combined partly as sodium bicarbonate, partly with the proteins of the blood plasma, and partly with hæmoglobin, the proportions in inorganic and organic combination being approximately equal. The proteins in the plasma can act either as weak acids or as weak alkalies, and as the blood passes through the lungs it loses carbonic acid and the proteins combine with the sodium thus set free; when the blood takes up carbonic acid from the tissues, the combination between sodium and protein is broken, and the carbonic acid unites partly with the sodium and partly with the protein. In this way, the reaction of the blood remains practically constant, in spite of the varying amount of carbonic acid which it contains.

Owing to this action of protein, when blood is exposed to a vacuum the whole of the carbonic acid which it contains is evolved, whereas when a pure solution of sodium bicarbonate is exposed to a vacuum only half the carbonic acid is evolved. In the former case the sodium enters into combination with the protein; in the latter it forms sodium carbonate, which is stable *in vacuo*.

The dissociation curve of carbonic acid in blood, when exposed to varying partial pressures of carbonic acid in the surrounding air, has the same general form as that of oxyhæmoglobin, the dissociation being most rapid when the partial pressure of carbonic acid varies from 0 to 30 mm. Hg. Oxygenated blood gives off its carbonic acid more readily than deoxygenated blood.

The blood also contains about $2\frac{1}{2}$ volumes of carbonic acid per 100 volumes of blood in solution.

THE EXCHANGE OF GASES IN THE LUNGS.

The air in the lungs is separated from the blood by the walls of the pulmonary capillaries and by the alveolar epithelium; and each of these membranes is extremely thin. Two theories have been held as to the means by which oxygen passes from the alveoli into the blood and carbonic acid from the blood into the alveoli. On the one hand, it has been supposed that the tension of oxygen in arterial blood is higher than that in the alveolar air, and that the pulmonary epithelium must therefore secrete oxygen into the blood. On the other hand, it is widely held that the tension of oxygen in arterial blood is always lower than that in the alveolar air, and that oxygen passes from the lungs into the blood by the purely physical process of diffusion. These divergent views arose from the fact that the observers employed

different methods to determine the tension of oxygen in arterial blood, and obtained discordant results.

An improved form of aërotonometer, which can be used to measure the tension of oxygen in circulating blood, has been devised by Krogh, and the lower part of it is shown in fig. 101. It consists of a cannula A, which is attached to the central end of an artery; the blood flows from the cannula into a bulb B, from the top of which passes off a narrow graduated tube. A small air bubble C is placed in the bulb, and the blood flows through the bulb and is returned to the distal end of the artery by the tube D, clotting being prevented by the injection of hirudin. An interchange of gases takes place between the blood and the bubble, and, owing to the small size and relatively large surface of the latter, the gases in the blood and the bubble soon come into equilibrium, this being reached when the size of the bubble remains constant; it is then withdrawn into the graduated tube, and its composition is analysed.

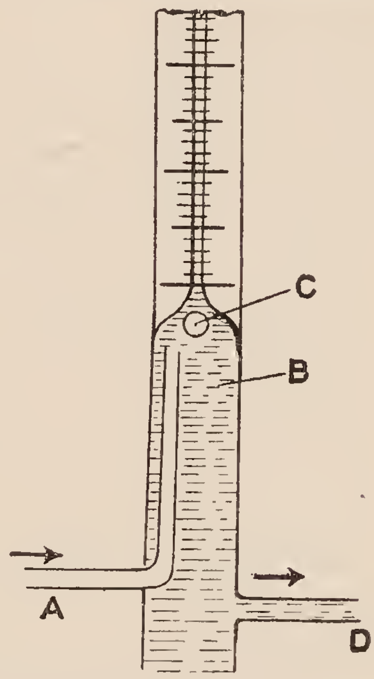


Fig. 101.—Krogh's tonometer.

Since the oxygen of the blood is in equilibrium with that in the bubble, the tension of oxygen in the blood can be ascertained by determining the percentage of oxygen in the bubble and the total pressure to which it is exposed. If the arterial pressure is 100 mm. Hg, and the bubble contains 10 per cent. of oxygen, the partial pressure of oxygen is 10 per cent. of 860 mm. Hg (atmospheric + arterial pressure), namely 86 mm. Hg. The tension of oxygen in the blood is thus equal to 86 mm. Hg, or about 11·3 per cent. of oxygen at atmospheric pressure.

By means of this apparatus, it has been found that in animals the tension of oxygen in arterial blood is distinctly less than that in alveolar air, the difference being usually 1 to 3 per cent. of an atmosphere (fig. 102). It has been estimated that in man the oxygen tension of venous blood is about 40 mm. Hg, whereas the partial pressure of oxygen in alveolar air is usually about 105 mm. Hg. Taking into account (1) the rate at which oxygen can diffuse through a membrane similar to that separating the blood from the alveolar air, and (2) the enormous surface area of the alveoli, it has been calculated that this difference in the tension of oxygen in the lungs and in the venous blood respectively is more than sufficient to provide for the passage of oxygen from the alveolar air into the blood by simple diffusion.

Although this view is generally accepted, some authorities are still

of opinion that it is true only for the resting individual, and that during exercise, when the need for oxygen is greater, or, at high altitudes, when the supply of oxygen is deficient, the tension of oxygen in the blood is higher than that of alveolar air, and that this difference is due to the secretion of oxygen into the blood by the pulmonary epithelium.

Similarly, it has been found that the tension of carbonic acid in venous blood corresponds with a partial pressure of about 46 mm. Hg, and is very slightly higher than that in alveolar air (fig. 102). If the

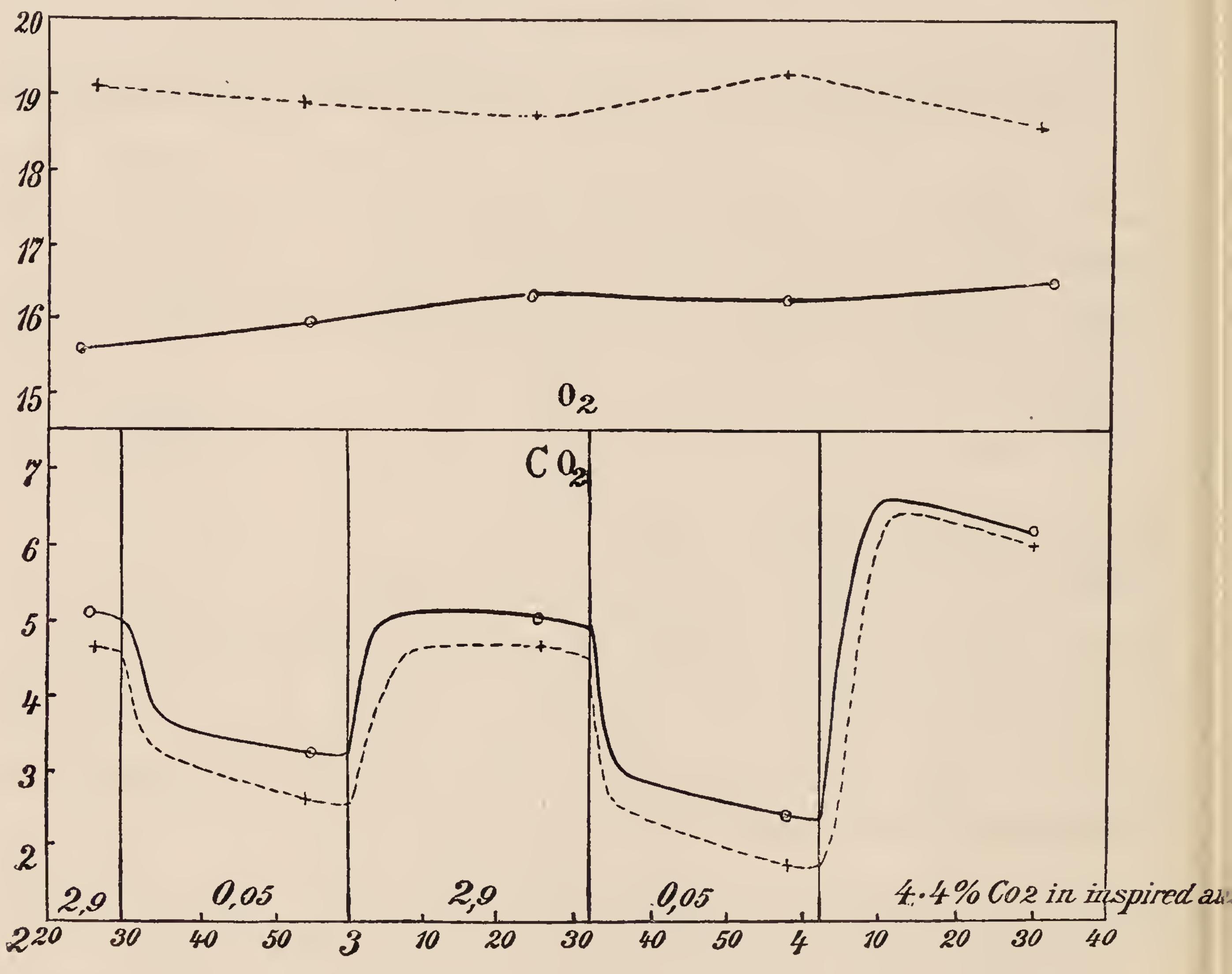


Fig. 102.—The tension of gases in the alveolar air and in blood. (Krogh.) From Barcroft, *Respiratory Function of the Blood.*

The dotted lines represent the tension in the alveolar air, and the continuous lines show the tension in the blood. During three periods the amount of CO_2 in inspired air was increased.

tension of carbonic acid in alveolar air is raised, the tension in the blood shows a corresponding rise and still remains slightly higher than that in the alveolar air.

In man the difference between the tension of carbonic acid in venous blood and in alveolar air is probably about 6 mm. Hg. This difference is much smaller than that between the tension of oxygen in alveolar air and venous blood respectively, but carbonic acid diffuses through a membrane such as that separating the air in the lungs from the blood, twenty-five times as quickly as oxygen ; and the difference between the

tension of carbonic acid in venous blood and in alveolar air, slight though it is, is sufficient to allow carbonic acid to pass from the blood into the air in the lungs by simple diffusion.

Owing to the difference in the tension of oxygen and of carbonic acid in the blood and in alveolar air, the venous blood as it flows through the lungs takes up oxygen and leaves the lungs almost fully saturated; at the same time it loses 6 to 8 volumes of carbonic acid per 100 volumes of blood.

SECTION III.

THE REGULATION OF THE RESPIRATORY MOVEMENTS.

Oxygen is continually passing from the alveolar air into the blood, and is replaced by the entrance of air from the atmosphere during respiration. Similarly, carbonic acid is constantly diffusing from the blood into the alveolar air, and with each expiration a certain amount is expelled from the lungs. Assuming that the amount of air entering and leaving the lungs with each breath is 400 c.c., and that the expired air contains 4 per cent. of carbonic acid, then with each respiration 16 c.c. of carbonic acid are removed from the body. Since the composition of alveolar air remains constant, it is evident that 16 c.c. of carbonic acid must, in the same time, have passed from the blood into the air in the lungs. When an additional amount of carbonic acid is formed in the body and taken up by the blood, it passes into the alveolar air and tends to raise its percentage. Hence, if the percentage of carbonic acid in alveolar air is to remain constant, as it actually does under normal conditions, the amount of air passing into and out of the lungs at each breath must be correspondingly increased. If 32 c.c. of carbonic acid pass from the blood into the alveolar air during a breath, they can be removed if the amount of expired air is 800 c.c. containing 4 per cent. carbonic acid. In the same way, the needs of the body for more oxygen are met by a larger amount of air entering the lungs at each inspiration. This process, whereby any accumulation of carbonic acid or deficiency of oxygen in the alveolar air, and consequently in the blood, is prevented, is under the control of the central nervous system, and is regulated in such a way that an excess of carbonic acid, or a lack of oxygen, leads to deeper and more rapid respiratory movements.

The Respiratory Centre.—The rhythmic alternation of inspiration and expiration is brought about by the contraction of the respiratory muscles, which are controlled and co-ordinated by a centre — the respiratory centre—lying in the grey matter of the floor of the fourth ventricle near the apex of the calamus scriptorius. From this centre,

impulses pass along the nerves supplying the respiratory muscles, namely, the vagus to the muscles of the larynx, the cervical nerves to the muscles of the neck, the intercostal nerves to the intercostal muscles, and the phrenic nerves to the diaphragm.

The centre is bilateral, each half controlling the muscles of the corresponding side, the two halves being connected by commissural fibres. Its position has been determined by observing the effect upon the respiratory movements of transection of the brain stem or spinal cord at various levels. When a section is made across the pons or medulla oblongata at any point above the level of the striæ acusticæ, respiration is unaffected. If the spinal cord is divided at the upper end of the cervical region, the respiratory muscles supplied by nerves above the section, *e.g.* those which dilate the alæ nasi, continue to contract. Destruction of the medulla oblongata, in the region of the apex of the calamus scriptorius, is at once followed by cessation of all respiratory movements. The region occupied by the centre is not sharply defined, but it is undoubtedly closely connected with the sensory nuclei of the vagus nerves.

There is no evidence of the existence of subsidiary centres in the spinal cord.

The centre continues to send out rhythmic impulses to the respiratory muscles when it is cut off from afferent impulses reaching it either from the higher parts of the brain or from the spinal cord. If, however, the brain stem is divided below the pons, and the vagus nerves are also divided, the respiratory movements are replaced by a series of inspiratory spasms, and the animal dies after a short time. It is doubtful, therefore, whether the centre can be regarded as acting automatically in the absence of all afferent impulses, though this view has been taken by some writers.

The question is one of theoretical rather than practical interest, since, in ordinary circumstances, a constant stream of afferent impulses is reaching the centre and modifying its activity; and hardly any nervous centre in the body is more easily influenced in this way than the respiratory centre. For instance, the mere directing of one's attention to the respiratory movements is sufficient to alter their rate or depth. The respiratory centre, like the vaso-motor centre, is also extremely sensitive to any changes in the composition of the blood supplying it. These two factors which modify its activity, namely, (1) the composition of the blood, and (2) nervous impulses from the higher centres or from the peripheral nerves, will be considered separately. The former affects primarily the depth, and the latter the rate of respiration.

Methods of Recording Respiratory Movements.—In order to study these changes, it is desirable to obtain a graphic record of the rate and depth of the respiratory movements; and numerous methods have been devised for this purpose.

(1) In man the respiratory movements can be recorded by a stethograph, one form of which consists of a small metal cylinder, provided with a lateral opening and closed at each end by a rubber membrane; the lateral opening is connected by rubber tubing with a tambour. Strings are attached to the centre of each rubber membrane, and are passed round the chest and tied. Each expansion of the chest causes the strings to pull upon the rubber membrane, so that the capacity of the cylinder increases and the lever of the tambour falls; during expiration the membranes return to their former position. The same apparatus can be used to record the respiratory movements in the lower animals.

(2) Another method, used in animals, is to connect the side piece of a cannula, inserted into the trachea, with a tambour; with each inspiration air is sucked out of the tambour, and the lever falls.

(3) In rabbits, a small slip of the diaphragm on each side is inserted into the xiphisternum; and by separating the xiphisternum from the sternum, this strip of muscle can be isolated without interfering with its vascular or nervous connections. It contracts synchronously with the rest of the diaphragm, and by connecting the xiphisternum with the membrane of a tambour by means of a thread, each contraction of the slip can be recorded and serves as an index of the movements of the diaphragm as a whole (Head's method).

THE CHEMICAL REGULATION OF RESPIRATION.

The two most important changes in the composition of the blood which alter the respiratory movements are: (1) variations in the tension of carbonic acid, and (2) a fall in the tension of oxygen.

(1) **The Tension of Carbonic Acid.**—If an animal is allowed to breathe air containing 2 to 3 per cent. carbonic acid, the respiratory movements become much deeper, and after a short time usually more frequent; such an experiment is illustrated in fig. 103. If the experiment is made on man, it is further found that the percentage of carbonic acid in the alveolar air remains constant. The immediate effect of breathing air containing an excess of carbonic acid is to increase the percentage in the alveolar air, thereby diminishing the passage of carbonic acid by diffusion from the blood into the air in the lungs. As a result, the tension of this gas in the blood rises; this increase in tension stimulates the respiratory centre to increased

activity, and the amount of air passing into and out of the lungs with each breath may be doubled or trebled. In this way a larger amount of carbonic acid is expelled from the lungs with each expiration, and the mean tension in the lungs is kept at the same level.

The centre is extremely sensitive to the slightest rise in the tension of carbonic acid in the blood, and a rise of 0·2 per cent. of an atmosphere in the pressure of this gas in alveolar air doubles the ventilation of the lungs, that is to say, the amount of air passing into and out of

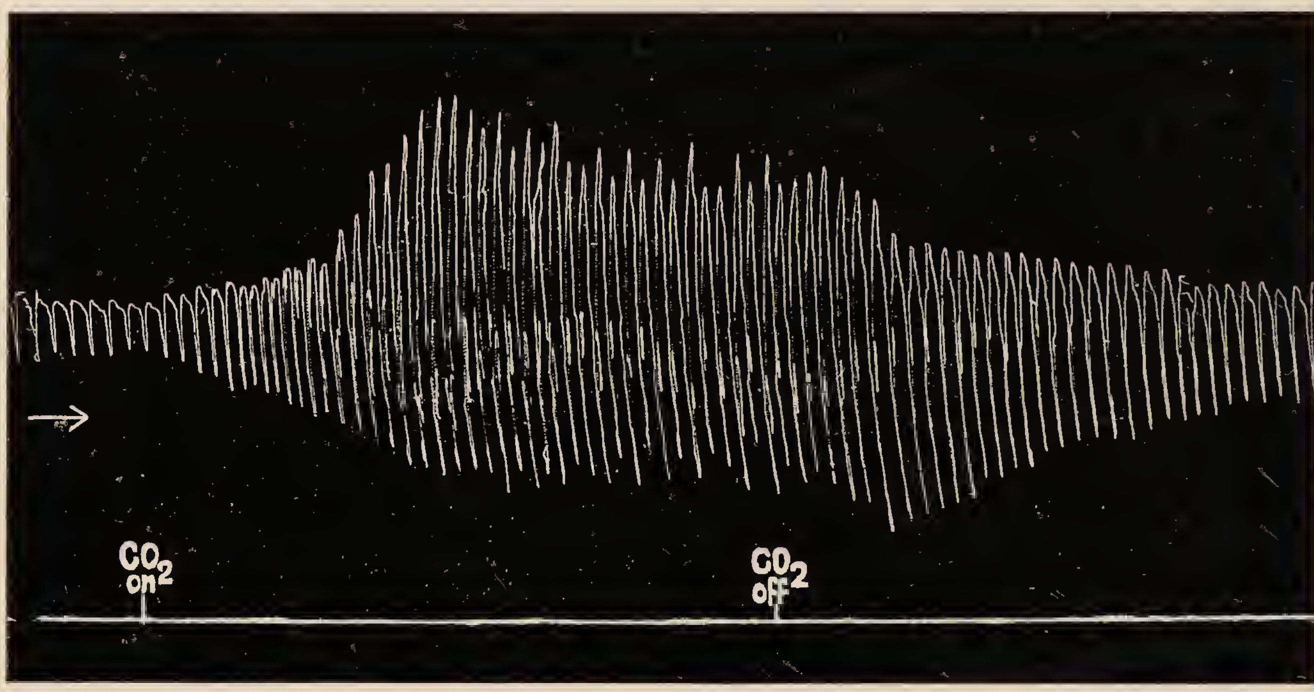


FIG. 103.—The effect of CO_2 on the respiratory movements in the normal animal. The inspired air contained 3 per cent. CO_2 during the period marked on the tracing.

them at each breath. The capacity of the respiratory centre to react to any increase in the tension of carbonic acid in the blood passing to it is very great, as is shown in experiments in which the amount of carbonic acid in the air breathed is gradually increased. As seen in the following table from Haldane, the percentage in alveolar air remains constant until the amount in the inspired air exceeds 3 per cent.; beyond this point the percentage of carbonic acid in the alveolar air rises, and the ventilation of the lungs becomes enormously increased.

Percentage of Carbonic Acid in Inspired Air.	Percentage of CO_2 in Alveolar Air.	Average Depth of Respirations in c.c.	Average Frequency of Respiration per Minute.	Ventilation of Alveoli. Normal taken as = 100.
0·03 per cent.	5·6 per cent.	673	14	100
1·52 ,,	5·55 ,,	793	15	137
2·02 ,,	5·6 ,,	864	15	153
3·07 ,,	5·5 ,,	1216	15	226
3·73 ,,	5·9 ,,	1330	14	273
5·14 ,,	6·2 ,,	1771	19	498
6·02 ,,	6·6 ,,	2104	27	857

The effect of carbonic acid in stimulating the respiratory centre is also seen during muscular exercise. During exercise the muscles form a large amount of carbonic acid, which passes into the blood and raises the tension of this gas in the blood. This rise of tension stimulates the respiratory centre, and the respiratory movements become deeper and more frequent, with the result that a larger amount of carbonic acid is carried off in the expired air. Most observers have found a considerable rise in the tension of carbonic acid in alveolar air during exercise. According to the recent observations of Krogh, however, the tension remains practically unaltered, and the response of the respiratory centre to the stimulus of carbonic acid is as delicately adjusted during exercise as during rest. As the result of several observations on the same person, Krogh obtained the following figures for the alveolar tension of carbonic acid :—

	Tension of Alveolar CO_2.
Rest	5·06
Exercise	5·10

We may, therefore, regard the regulation of the respiratory movements and of the amount of air passing into and out of the lungs as dependent, under normal conditions, upon the tension of carbonic acid in the blood which supplies the respiratory centre; and since the tension of carbonic acid in the respiratory centre itself must vary with that in the blood, the ultimate stimulus to the respiratory movements is evidently the tension of carbonic acid in the respiratory centre.

Since the slightest rise in the tension of carbonic acid in the blood increases the respiratory movements, a diminution might be expected to lessen the respiratory movements by diminishing or abolishing the stimulus to the centre; and such is found to be the case.

When an individual takes a number of deep breaths (forced respiration), more carbonic acid is removed from the lungs than is entering them from the blood. Hence the tension in alveolar air, and in blood, falls to such a level that it no longer stimulates the respiratory centre; and respiration ceases for a short time (apnœa). During the period of apnœa, carbonic acid continues to reach the blood from the tissues, and the tension in the blood and in the alveolar air gradually rises, until it again reaches a level sufficient to stimulate the respiratory centre; when this occurs respiration recommences (fig. 111).

Apnœa can also be produced in animals by repeated inflation of the lungs, whereby carbonic acid is, so to speak, washed out of the lungs and its tension in the alveolar air falls.

A marked fall in the tension of carbonic acid in the alveoli gives rise

to the condition known as *acapnia*, in which the blood pressure is very low and the tone of the muscular walls of the digestive tract and of other unstriped muscles is lost; the symptoms closely resemble those of surgical shock (p. 235).

The activity of the respiratory centre is excited, not only by a rise in the tension of carbonic acid, but also by the addition to the blood of other acids, such as lactic acid. When 0·02 to 0·04 per cent. lactic acid is added to the blood, a considerable increase is produced in the depth of the respiratory movements even though the tension of carbonic acid in the blood is unaltered. It has been shown, indeed, that carbonic acid stimulates the respiratory centre, not in a specific manner, but because it is an acid and increases the concentration of H ions in the blood. Any other acid, by acting in the same manner, produces the same effect, and when lactic acid is added to the blood the centre is stimulated by the combined effect of this acid and of the carbonic acid already present in the blood. Since the respiratory movements are increased without any corresponding rise in the production of carbonic acid, the tension of carbonic acid in the blood and alveolar air falls.

(2) **The Tension of Oxygen in the Blood.**—The normal tension of oxygen in alveolar air is 105 to 110 mm. Hg. At this tension the blood leaving the lungs is almost fully saturated with oxygen, and the dissociation curve of blood (p. 258) shows that, even when the oxygen tension is reduced to 70 mm. Hg, the blood still contains 90 per cent. of its hæmoglobin as oxyhæmoglobin. Experiment shows, in fact, that atmospheric air containing only 12 to 13 per cent. oxygen, which corresponds with about 8 per cent. oxygen in the alveolar air, can be breathed without discomfort and without any alteration in the respiratory movements. When the percentage of oxygen in alveolar air falls below this figure, the breathing becomes deeper and considerable hyperpnœa may be produced. At the same time, the individual becomes cyanosed and may feel giddy, or may even lose consciousness.

These symptoms are the result of the imperfect oxygenation of the blood. The mere lack of oxygen in itself does not act as a stimulus to the respiratory centre, and the hyperpnœa is caused indirectly by the passage of lactic acid into the blood. Lactic acid is normally formed in the body, and in the presence of an adequate supply of oxygen it is subsequently oxidised to carbonic acid and water. When the supply of oxygen is insufficient, the lactic acid passes into the blood, and, by increasing its H ion concentration, stimulates the respiratory centre; the respiratory movements become deeper, and more air enters the lungs at each breath. The deeper breathing raises the tension of oxygen in the alveolar air, and thus increases the amount of oxygen

taken up by the blood. Thus the lactic acid, by producing hyperpnœa, serves to protect the tissues from the ill effects of a lack of oxygen.

The presence of an excess of oxygen in alveolar air has no effect on the respiratory movements, and wide variations may occur in the partial pressure of oxygen in the alveolar air without any appreciable change taking place in the respiration; even when pure oxygen is breathed, respiration is unchanged in a healthy individual. It is evident, therefore, that, provided the supply of oxygen is adequate, the depth of the respiratory movements is normally regulated by the tension (partial pressure) of carbonic acid in the alveolar air and in the blood.

Effect of Changes in Partial Pressure of Oxygen and Carbonic Acid.

	Barometric Pressure.	Percentage of CO_2 in Dry Alveolar Air.	Percentage of O_2 in Dry Alveolar Air.	Alveolar Pressure of CO_2 in Percentage of an Atmosphere.	Alveolar Pressure of O_2 in Percentage of an Atmosphere.
1	646·5 mm. Hg	6·61	13·19	5·23	10·41
2	755 ,,	5·95	13·97	5·53	13·06
3	1260 ,,	3·52	16·79	5·64	28·84

Further, this tension is extremely constant, though, as shown in the foregoing table, the actual percentage of carbonic acid in the lungs varies with the barometric pressure.

For example, when the barometric pressure is 1260 mm. Hg, the alveolar air contains 3·52 per cent. carbonic acid; this represents a partial pressure of $\frac{3{\cdot}52 \times 1260}{760} = 5{\cdot}6$ per cent. at 760 mm. Hg pressure.

ASPHYXIA.

The effects of a rise in the tension of carbonic acid and of lack of oxygen in the blood are seen in their most extreme form in asphyxia, and affect not only the respiratory, but also the circulatory system. Asphyxia may be brought about by occlusion of the trachea, by the absence of oxygen in the air breathed, and in other ways, and three stages are usually described.

(1) **Stage of Hyperpnœa.**—During this period, which lasts from ½ to 1 minute, the respiratory movements gradually increase in depth, and soon involve not only the muscles usually employed in respiration, but also the accessory muscles. The respiratory movements during this stage are co-ordinate, and show an alternate inspiratory and expiratory rhythm. Consciousness is lost at the end of this stage; the

expiratory movements become more and more exaggerated, and the first stage passes into

(2) **The Stage of Expiratory Convulsions.**—During this period every muscle which can assist expiration is called into action, and at the same time convulsive movements of the limbs take place. This period lasts about a minute, and is succeeded by

(3) **The Stage of Exhaustion**, during which the animal lies passive, the muscles are flaccid except for an occasional deep inspiration, the pupils are widely dilated, and all reflexes are absent. The respiratory movements become less frequent, and at the end of $1\frac{1}{2}$ to 2 minutes death takes place. The blood after death is almost free from oxygen.

If the blood pressure is observed in an animal during asphyxia, the vagi being cut, it may be seen that towards the end of the first stage the blood pressure rises rapidly, and soon reaches a very high level, which is maintained for a short time; towards the end of the second stage it begins to fall, and continues to fall steadily until the animal dies.

This sequence of events is brought about in the following manner. At the beginning of asphyxia, the accumulation of carbonic acid in the blood excites the respiratory centre, producing hyperpnœa. Towards the end of the first stage the increasing deficiency of oxygen begins to make itself felt, leading to the further stimulation of the respiratory centre and to loss of consciousness. In the second stage, the lack of oxygen stimulates the whole of the central nervous system, giving rise to the general convulsions which are observed; this effect is soon succeeded by paralysis, resulting from the prolonged deficiency of oxygen, and ending in death.

The vascular changes are also due partly to excess of carbonic acid, partly to lack of oxygen, as is shown in figs. 104 and 105. These figures make it clear that a rise of blood pressure similar to that seen in asphyxia (fig. 104, A) is produced either when the animal is allowed to breathe air containing no oxygen and no excess of carbonic acid (fig. 104, B), or when it breathes air containing an adequate supply of oxygen and a large excess of carbonic acid (fig. 105, A), or, finally, when lactic acid is injected into the circulation (fig. 105, B).

The rise of blood pressure is due to stimulation of the vaso-motor centre, which produces general constriction of the arterioles; adrenalin also is set free into the blood stream, and contributes to the rise of pressure. By enclosing a loop of intestine in a plethysmograph it may be shown that, with the onset of asphyxia, the volume of the loop diminishes owing to constriction of its blood-vessels, and that this constriction persists until the death of the animal. The final fall of blood pressure must be due, therefore, to failure of the heart; owing partly

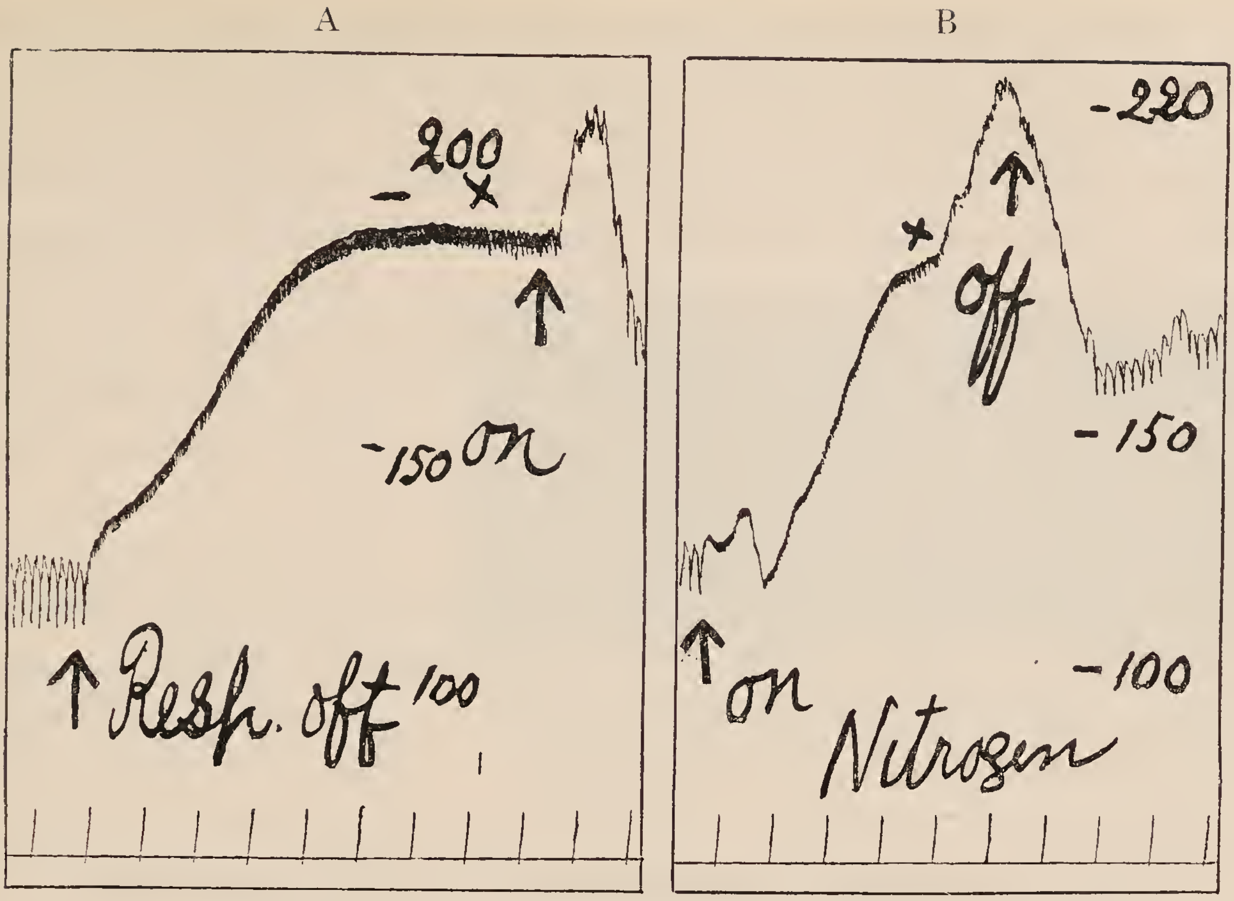


FIG. 104.—Blood-pressure tracing. (Mathison.)

A shows the effect of asphyxia; B shows the effect of breathing pure nitrogen.

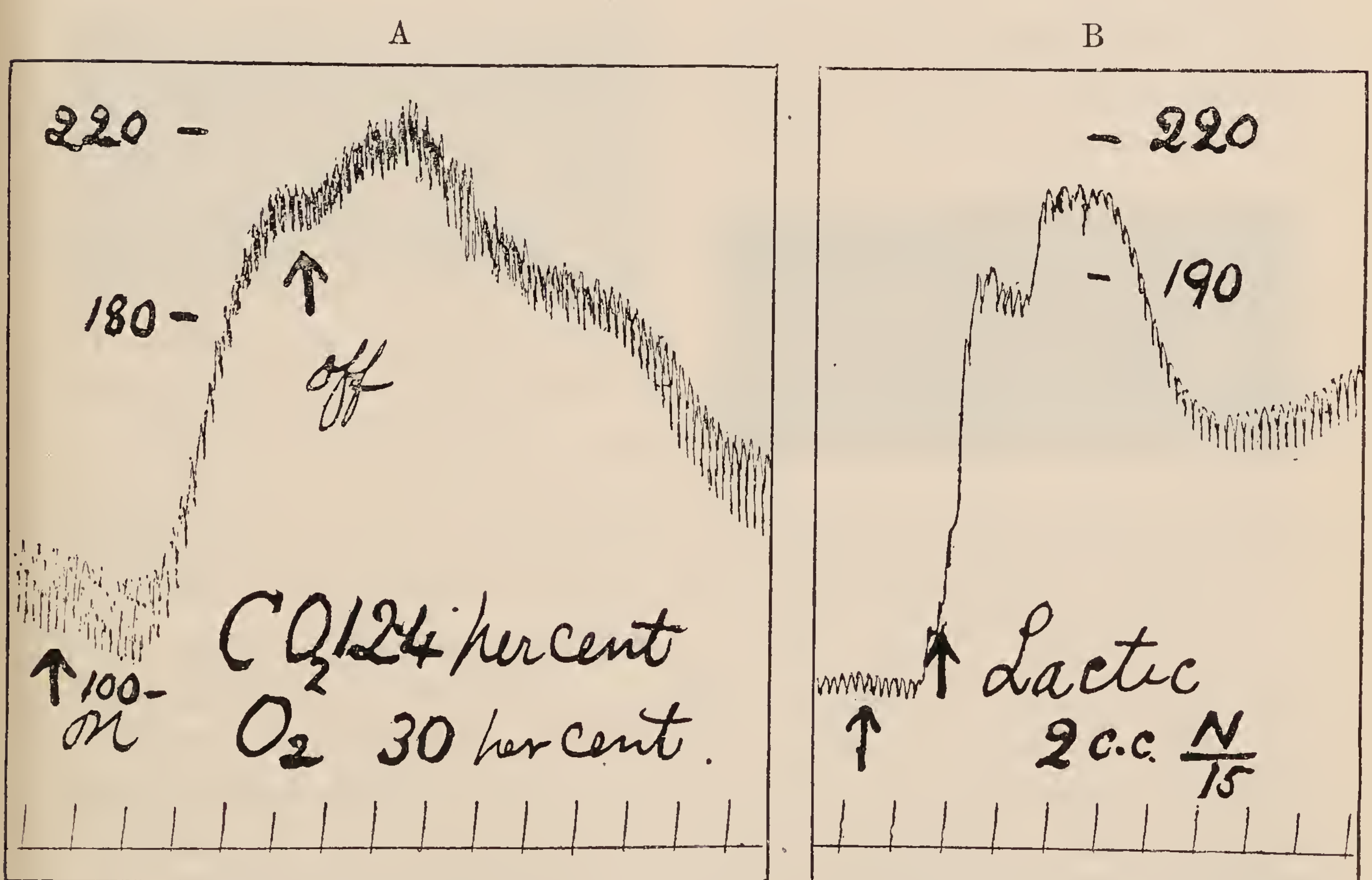


FIG. 105.—Blood-pressure tracing. (Mathison.)

A shows the effect of excess of CO_2 in inspired air; B shows the effect of injecting lactic acid into the circulation.

to the resistance offered by the high blood pressure, partly to the direct effect of lack of oxygen upon the nutrition of the heart itself, its output gradually diminishes, it becomes more and more distended, and finally ceases to beat. When the vagus nerves are intact, the vaso-constriction leads to reflex slowing of the heart, and the rise of blood pressure is smaller; the slowing of the heart lessens the strain thrown upon it, and life is prolonged for a minute or so longer. During asphyxia the conductivity of the bundle of His is often diminished, producing a condition of heart block, so that the auricles may beat twice or thrice as frequently as the ventricles.

The increased activity of both the respiratory and vaso-motor centres in asphyxia is, undoubtedly, the result of increased H ion concentration of the blood; it must be noted, however, that the respiratory centre is the more sensitive, and may be excited by an excess of carbonic acid too slight to affect the vaso-motor centre.

THE NERVOUS REGULATION OF RESPIRATION.

The respiratory centre can be influenced by nervous impulses reaching it (1) along the vagus, (2) from the higher parts of the brain, and (3) from other afferent nerves; the impulses affect primarily the frequency of the respiratory movements.

(1) **The Vagi.**—The influence of the vagus nerves is most easily studied in the rabbit, by recording the movements of an isolated slip of the diaphragm (p. 265). When a record of the respiratory movements is obtained by this method, it may be seen that division of the vagus nerve is followed by a decrease in the frequency of respiration, although each breath is deeper than before. Electrical stimulation of the central end of one vagus may then produce one of two effects upon the respiratory movements. Sometimes, especially with a weak stimulus, or with a constant ascending current, the inspiratory movements are inhibited (fig. 106), and the slip of diaphragm remains in the expiratory position, that is, it is relaxed. More often the inspiratory movements are increased (fig. 107), as is shown by the fact that the diaphragm contracts and may remain in the inspiratory position.

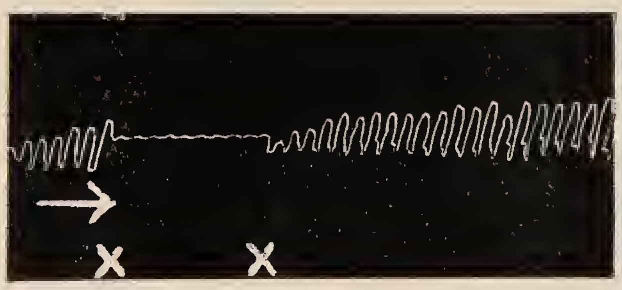


FIG. 106.—Stimulation of central end of one vagus between X and X. The slip of diaphragm remains in the relaxed, expiratory condition.

These experiments make it clear, first, that the vagus contains afferent fibres carrying impulses to the respiratory centre, which

modify the rate of respiration, and, secondly, that these impulses are of two kinds, one tending to cause inspiration and the other expiration. These fibres have their origin in the lungs, and their endings can be stimulated by inflating, or sucking air out of, the lungs. Fig. 108 illustrates the effect of suddenly distending the pulmonary alveoli with air; the diaphragm remains relaxed, inspiratory movements cease, and the whole chest is in the expiratory position. This effect, which is produced only when the vagus nerves are intact, and lasts only as long as the distension persists, is known as *vagus apnœa.* Conversely, when air is sucked out of the lungs (negative ventilation) the diaphragm is thrown into contraction, and the inspiratory movements are increased.

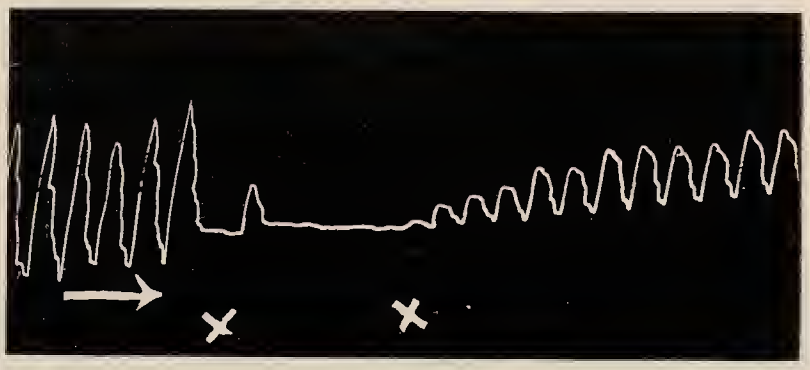


FIG. 107.—Stimulation of the central end of one vagus between X and X. The diaphragm enters into continued contraction (inspiratory position).

It is evident that distension of the pulmonary alveoli stimulates the endings in the lungs of afferent fibres which pass up the vagus to the respiratory centre, and inhibits inspiration and brings about expiratory movements. On the contrary, collapse of the pulmonary alveoli stimulates the endings of afferent fibres running in the vagi and conveying impulses to the respiratory centre whereby inspiratory movements are evoked.

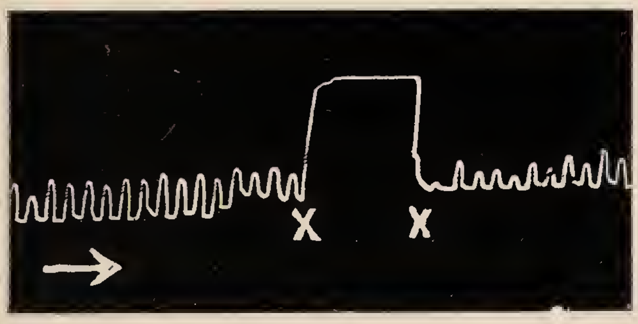


FIG. 108.—Apnœa produced by sudden distension of the lungs between X and X. The vagi are intact.

The existence of such impulses can be further demonstrated by connecting the vagus with a string galvanometer; with each inspiration a deflection of the thread takes place, which indicates the passage of an impulse along the nerve; and, under certain conditions, a similar deflection may also be observed during expiration. In normal respiration these two sets of fibres are alternately stimulated, each inspiration sending impulses along one set of fibres and reflexly causing expiration, whereas each expiration gives rise to impulses which bring about another inspiration. The electrical variations in the vagus seem to show that the impulses leading to expiration are the more important and more pronounced.

Although these impulses help to maintain the normal rhythm of the

respiratory movements, they are not essential, and respiration continues after they are prevented from reaching the respiratory centre by division of the vagi. Their principal function seems to be that of rendering the centre more sensitive to the normal stimulus of carbonic acid, and of controlling the respiratory discharge from the centre to the respiratory muscles. In their absence, the respiratory centre is not stimulated until the tension of carbonic acid in the blood rises higher than in the normal animal, although the resulting respiration, when it does occur, is exceedingly forcible; moreover, the normal adjustment of the respiratory movements in response to any considerable increase in the

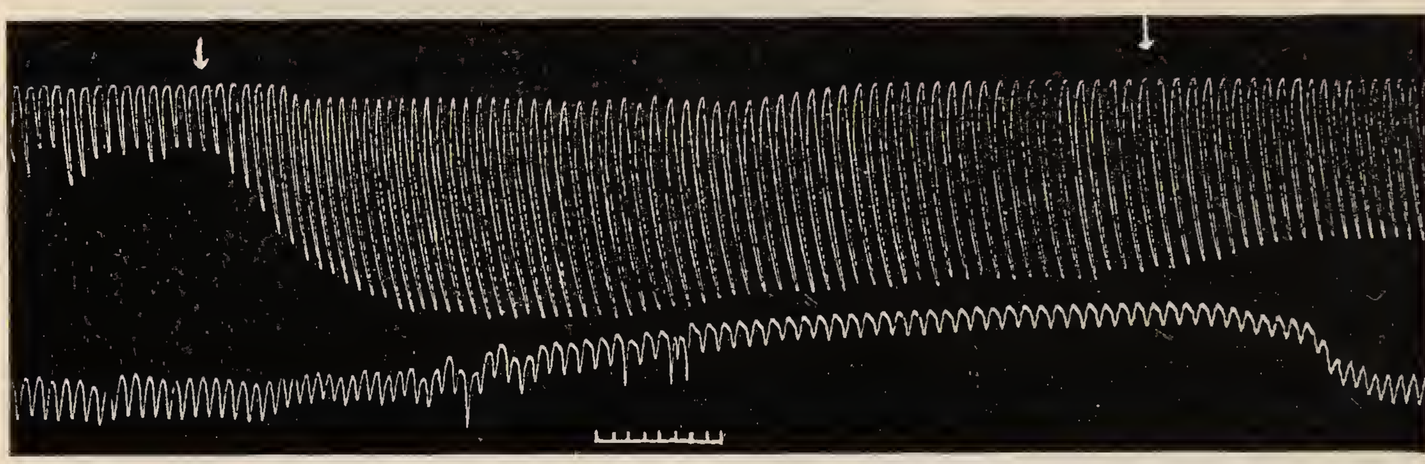


Fig. 109.—Respiratory movements in rabbit with vagi divided. Between the arrows, the inspired air contained 10 per cent. CO_2. Note that the *rate* of respiration is not increased. (Scott.)

tension of carbonic acid in alveolar air and blood is no longer efficiently carried out.

During muscular exercise, for example, a normal animal breathes not only more deeply, but also more frequently, and is thus able to expel from the lungs all the additional carbonic acid reaching them from the blood; after section of the vagi the rate of respiration remains unaltered, the ventilation of the lungs is inadequate, and the percentage of carbonic acid in the alveolar air rises. The same result is seen when an animal, with its vagi divided, breathes air containing an excess of carbonic acid (fig. 109), the ventilation of the lungs being much less than in the normal animal, as is seen in the following table:—

Ventilation of the Lungs.

Composition of Inspired Air.	Total Ventilation per Minute.	
	Normal Rabbit.	Rabbit with Vagi Divided.
(1) Atmospheric air . .	1368 c.c.	1305 c.c.
(2) Air to which 8·6 per cent. CO_2 was added . .	2813 ,,	1596 ,,

(2) **Impulses from the Higher Parts of the Brain.**—In an anæsthetised animal, the brain stem may be divided in the pons or upper part of the medulla without any obvious change being produced in the respiratory movements. Nevertheless, impulses from the higher parts of the brain can greatly modify respiration, and the effect on respiration of emotional states, such as anger or excitement, is often very marked.

Again, the respiratory movements become deeper and more frequent at the very beginning of severe muscular exercise; even the first breath taken after the onset of muscular work is much deeper than the respiration during rest (fig. 110). These changes occur too quickly to be

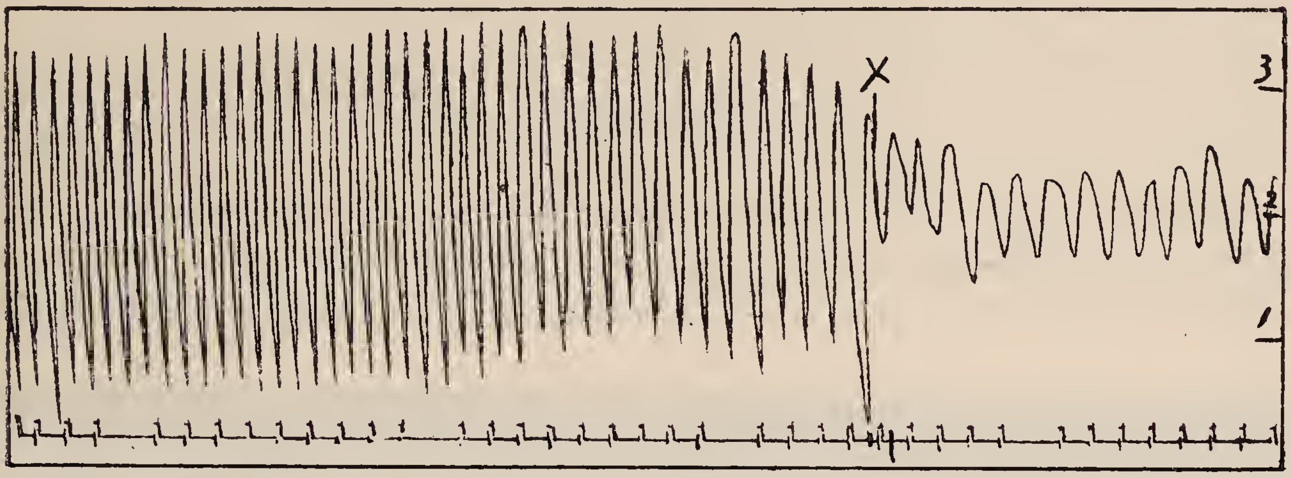


FIG. 110.—Effect of muscular work on the respiratory movements. (Krogh.) The work begins at X. Tracing to be read from right to left.

brought about by an increase in the tension of carbonic acid in the blood, and recent observation shows that they are due to impulses passing from the cerebral cortex to the respiratory centre, which render it more sensitive than before to the presence of carbonic acid in the blood. Hence the normal tension of carbonic acid, acting on the unusually sensitive centre, calls forth deeper and more rapid respirations. By this means the amount of oxygen entering the lungs and passing to the blood and tissues is increased at the very beginning of exercise; and the muscles are able to take up from the blood, without delay, the additional oxygen which they need for their increased activity.

(3) The respiratory movements may also be modified by impulses reaching the centre from almost every region of the body. Thus painful stimuli usually produce hyperpnœa, whereas impulses passing along the fifth nerve and the nerves from the upper respiratory passages tend to inhibit respiration; these nerves may be stimulated by irritant vapours, such as that of ammonia. The superior laryngeal nerve supplies sensory fibres to the glottis; and stimulation of its endings, for instance, by the entrance of a crumb into the glottis, inhibits inspiration and causes violent expiratory efforts. Electrical stimulation of the central end of the nerve brings about the same effect.

Summarising the various factors which influence respiration, we see, first, that the normal stimulus to the respiratory centre is the tension of carbonic acid in the blood passing to the centre: an increase of this tension stimulates the centre, and when the tension falls respiration ceases. Secondly, when the blood is deficient in oxygen, lactic acid passes into the blood and also stimulates the centre. Thirdly, impulses passing along the vagus nerves from the lungs help to maintain the normal rhythm of respiration, and make the centre more sensitive to the chemical stimulus of carbonic acid. Finally, impulses from the higher parts of the brain, or impulses reaching the centre by afferent nerves may, and do, modify the respiratory movements.

APNŒA.

Reference has already been made to the inhibition of the respiratory movements, which is known as apnœa. The most important condition which gives rise to apnœa is a fall in the tension of carbonic acid in the

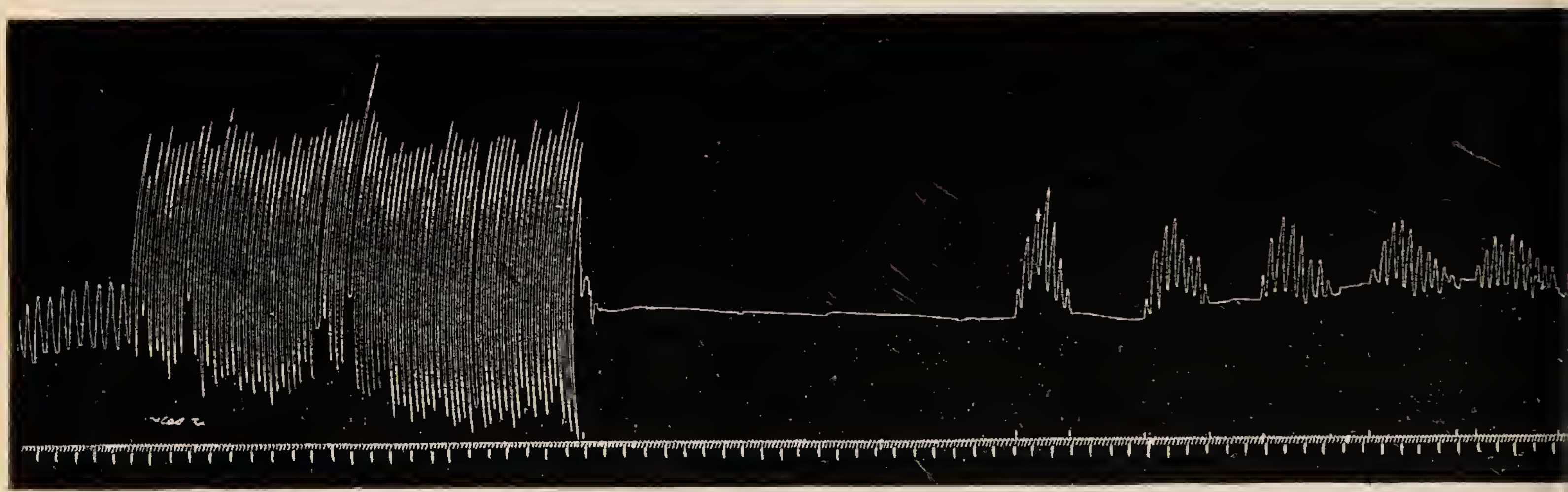


FIG. 111.—Forced breathing in man, followed by apnœa and subsequently by Cheyne-Stokes breathing. (Haldane and Douglas.)

blood; this occurs whenever the ventilation of the lungs is increased without any corresponding rise in the production of carbonic or lactic acid in the body, and may therefore be brought about either, in man, by voluntary forced breathing (fig. 111), or, in animals, by vigorous artificial respiration. In these circumstances the apnœa may last for 1 to 2 minutes, respiration beginning again as soon as the tension of carbonic acid in the alveolar air returns to its normal level. That it is due solely to a fall in the tension of carbonic acid is clearly shown by the fact that, when the inspired air contains an excess of carbonic acid, forced breathing is not followed by apnœa.

A totally different form of apnœa is that produced by sudden distension of the lungs, and known as vagus apnœa (p. 273). This is

due to the stimulation of the endings in the lungs of the afferent fibres of the vagus which inhibit inspiration.

Apnœa also occurs during deglutition, and lasts for a period of about 6 seconds; the afferent impulses pass along the glossopharyngeal nerve. The effect of this inhibition is to prevent particles of food being drawn into the lungs by an inspiratory act during the process of swallowing.

Another interesting example of the adaptation of the respiratory mechanism to the needs of the animal is seen in ducks. When a duck plunges its head into water in search of food, the respiratory movements are inhibited; and this form of apnœa can be reproduced experimentally by placing the duck in the vertical position with its head downwards. The afferent impulses which travel to the respiratory centre and inhibit respiration arise in the muscles of the neck and in the labyrinth of the ear; after section of the afferent nerves from these muscles or destruction of the labyrinth, this form of apnœa can no longer be evoked.

CHEYNE-STOKES BREATHING.

This form of breathing (fig. 112), which is not infrequently observed in human beings living at high altitudes or suffering from various diseases, more especially those affecting the circulatory system, has the following characters. After an apnœic pause respiration begins, the breaths being shallow at first and gradually increasing in depth till they reach a maximum. They then become smaller, and in a short time cease altogether, being succeeded by a period of apnœa. Cheyne-Stokes breathing can also be produced experimentally in healthy persons as a result of prolonged forced breathing, as is seen in fig. 111; the immediate effect of the forced breathing is a period of apnœa, and when breathing recommences, it often exhibits the periodic character just described.

The phenomenon is caused by lack of oxygen in the blood. During the period of forced breathing, the tension of carbonic acid in the alveolar air falls considerably, leading to prolonged apnœa, during which the oxygen tension in the blood sinks and the supply to the respiratory centre is inadequate; as a result lactic acid is formed in the respiratory centre, and, together with carbonic acid, stimulates the respiratory centre, although the tension of carbonic acid alone is insufficient. Respiration begins again, and the oxygen taken into the lungs and into the blood oxidises the lactic acid. At the same time, however, the deeper breathing removes some carbonic acid from the lungs, the chemical stimulus to respiration again disappears, and the

breaths become smaller and finally stop. During the next apnœic pause, the blood again becomes deficient in oxygen, and a fresh formation of lactic acid takes place in the respiratory centre.

When this form of breathing occurs in disease, it can be removed either by allowing the patient to breathe nearly pure oxygen, which improves the nutrition of the respiratory centre and prevents the formation of lactic acid, or by the administration of air containing a slight excess of carbonic acid, which, by raising the tension of this gas

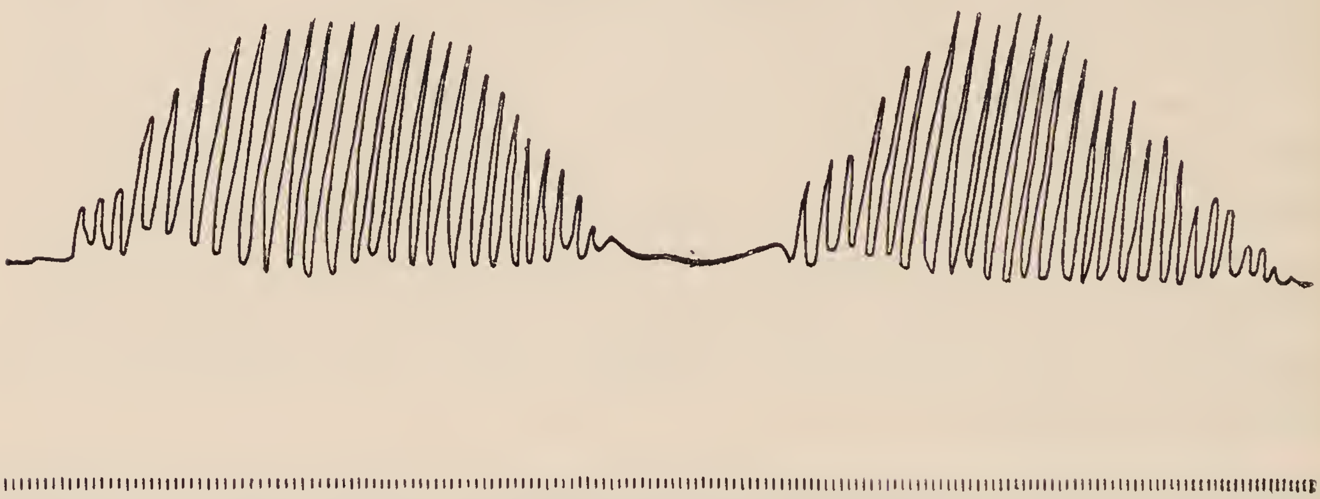


Fig. 112.—Cheyne-Stokes respiration. (Pembrey and Allen.) From *Practical Physiology*, by Pembrey and others.

in the alveolar air and blood, increases the strength of the stimulus to the respiratory centre.

SECTION IV.

TISSUE RESPIRATION.

The processes of external respiration, which have been thus far considered, are so adapted that the blood, when it reaches the capillaries, is almost fully saturated with oxygen. More important, however, is tissue respiration, which consists in the transference of oxygen from the blood to the tissues and the return of carbonic acid from the tissues to the blood.

Oxygen passes from the blood to the tissues by diffusion, and the amount which is available for the tissues depends largely upon the extent to which oxygen is set free in the plasma by the dissociation of oxyhæmoglobin. If the tension in the tissues were zero, as was formerly supposed, the conditions during the passage of blood through the capillaries would be the same as if it were exposed to a vacuum, and the dissociation of oxyhæmoglobin would be almost complete. Recent observations have shown, however, that the actual tension of oxygen in the tissues varies from 10 to 40 mm. Hg, being highest in the glandular

tissues and least in the muscles; this tension is so low that, as the blood traverses the capillaries, its oxyhæmoglobin undergoes dissociation to a considerable extent. The oxygen thus set free passes into solution in the blood plasma and diffuses into the tissues. Further, the *rate* at which oxyhæmoglobin dissociates at this tension is increased by the addition to the blood of carbonic acid, and often of lactic acid, as it passes through the capillaries.

In addition to these two factors, the amount of oxygen available for the use of the tissues depends upon the rate at which the blood is flowing through the capillaries.

Carbonic acid also passes by diffusion from the tissues, in which its tension is high, into the plasma, in which its tension is much lower. The tension of carbonic acid in the tissues is ascertained indirectly by measuring its tension in bile or urine, and is about 8 to 9 per cent. of an atmosphere, whereas its tension in blood is only 5 to 6 per cent. of an atmosphere.

The Consumption of Oxygen by the Tissues.—The tissues are constantly taking up oxygen, and the amount used by any tissue, for example the kidney, can be determined by ascertaining, first, the difference in the quantity of oxygen present in 1 c.c. of the blood entering and leaving the organ respectively; secondly, the amount of blood flowing through the organ in a given time; and, thirdly, the weight of the organ. The degree to which the blood is saturated with oxygen is measured by Barcroft's blood-gas manometer. The rate of blood flow through the organ is ascertained by observing directly the quantity escaping from it in a given time. To take an example, if 1 c.c. of arterial blood contains 0·18 c.c. oxygen, and 1 c.c. of blood from the renal vein contains 0·13 c.c. of oxygen, each c.c. of blood passing through the kidney loses 0·05 c.c. oxygen. Supposing the rate of blood flow through the kidney to be 50 c.c. per minute, the amount of oxygen taken up by the kidney cells is 2·5 c.c.; and if the weight of the kidney is 30 grams, 1 gram of kidney uses 0·08 c.c. oxygen per minute. Experiments made in this way show that the amount of oxygen consumed by the different tissues of the body varies greatly; the heart and kidney use more oxygen than any other organ.

O_2 CONSUMED BY 1 GRAM OF THE TISSUE PER MINUTE.

Skeletal muscle (resting)	0·003 c.c.
,, ,, (active)	0·03 c.c.
Heart muscle	0·05 c.c.
Kidney	0·03–0·06 c.c.
Submaxillary gland (resting) . . .	0·023 c.c.

Provided that the flow of blood to an organ is sufficient to supply the amount of oxygen which it needs, a further increase in the flow of blood through it does not increase the consumption of oxygen. For instance, the rate of blood flow through the submaxillary gland may be increased tenfold without any rise taking place in the oxygen consumption of the gland. The oxygen consumption rises, however, whenever the functional activity of a tissue becomes greater, and in the case of skeletal muscle it may be increased tenfold during and just after muscular contraction. A similar rise occurs when the heart does more work, or when the secretory activity of the submaxillary and other glands is evoked.

OXYGEN CONSUMED BY THE SUBMAXILLARY GLAND.

	Oxygen Used by 1 grm. of Gland per Minute.	Rate of Blood Flow through the Gland in c.c. per Minute.
(1) Resting . . .	0·023 c.c.	0·35 c.c.
(2) Resting, with dilated blood-vessels . .	0·024 ,,	3·5 ,,
(3) During the secretion of saliva . . .	0·11 ,,	...

The increased consumption of oxygen occurs not only during the period of secretion or of muscular work, but for some time after this is

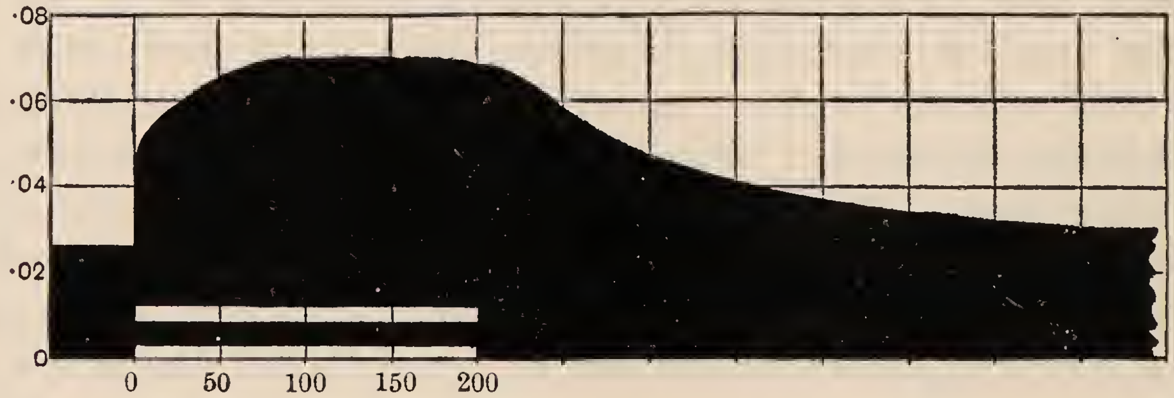


FIG. 113.—Ordinate = volume of oxygen used in c.c. per minute; abscissa = time in seconds; upper signal = duration of flow of saliva; lower signal = duration of chorda stimulation. Blackened area represents the oxygen used by the salivary gland. (From Barcroft, *Respiratory Function of the Blood.*)

over (fig. 113); and the oxygen is apparently used mainly in the carrying out of chemical changes, whereby the gland or muscle stores up potential energy and is restored to its previous condition. Every increase in the functional activity of an organ is also accompanied by dilatation of its blood-vessels, which, as already mentioned (p. 236), is

brought about by the action of the metabolic products set free in the tissue upon the vessels of the organ; this increases the supply of blood and, therefore, of oxygen to the active tissues.

The oxidative changes in the body normally take place in the tissue cells and not in the blood itself. When methylene blue is injected into an animal and the animal is killed a few minutes later, the blood is coloured blue, whereas the tissues show no change of colour. Although methylene blue is a comparatively stable substance, the avidity of the tissues for oxygen is so great that they are able to reduce it with the formation of a colourless reduction product. On exposing the tissues to the air, methylene blue is re-formed, and the tissues become deeply stained.

Another method of demonstrating the fact that oxidation does not take place in the blood is to allow it to stand for a short time, and to observe whether any of its oxyhæmoglobin is reduced. In normal animals the reduction is almost negligible, and evidently no oxygen is used up in carrying out metabolic changes in the blood itself.

SECTION V.

THE EFFECT OF CHANGES IN BAROMETRIC PRESSURE.

(1) **The Effect of Lowered Pressure.**—When a person ascends from near sea level to a height of 5,000 to 10,000 feet or more, he is apt to suffer from symptoms which are generally described as *mountain sickness*: these symptoms are headache, mental confusion, blueness of the lips, and nausea or vomiting. They may occur when the individual ascends to this height in a train, and are therefore not due to muscular exercise, although they may become more severe when exercise is taken. They are caused entirely by lack of oxygen. With increasing altitude the barometric pressure, and therefore the partial pressure of oxygen in the atmosphere and in the alveolar air, gradually fall; and when the alveolar pressure of oxygen falls to about 60 mm. Hg, the symptoms just described make their appearance. Similar symptoms are produced in animals and in man, when they are placed in closed chambers and the barometric pressure is gradually reduced. If the individual remains at a high altitude, the symptoms pass off in the course of a day or two, and after a time exercise may be taken without their recurrence.

The adaptation of the body to the altered conditions is brought about by changes in both the circulatory and respiratory systems. In the first place, the lack of oxygen leads to the passage into the blood of

lactic acid, which stimulates the respiratory centre; and the breathing becomes deeper, with the result that the partial pressure of carbonic acid in the alveoli decreases and that of oxygen rises. At a high altitude, when the alveolar oxygen pressure is low, even a small rise in the partial pressure of oxygen appreciably increases the extent to which hæmoglobin can be saturated with oxygen as the blood passes through the lungs. For example, if the alveolar pressure of the oxygen rises from 40 mm. Hg to 45 mm. Hg, the saturation of hæmoglobin may be increased from 70 per cent. to 75 per cent. At the same time, acceleration of the heart takes place, and consequently the blood is carried more rapidly through the lungs and round the body.

Owing to these changes, the blood not only takes up more oxygen in the lungs, but transfers it more rapidly from the lungs to the tissues. The presence of lactic acid also assists the dissociation of oxyhæmoglobin in the capillaries, so that more oxygen is available for the tissues.

Secondly, a more gradual compensatory process takes place in persons who remain at a high altitude for a long period. The number of red corpuscles and the percentage of hæmoglobin in the blood are increased, and the oxygen-carrying capacity becomes much greater. In one series of observations, made at a level of 14,000 feet, the percentage of hæmoglobin in the blood rose in the course of some weeks from 115 to 154. When the subjects returned to a low level, the percentage of hæmoglobin rapidly fell to normal.

The extent to which adaptation takes place varies in different individuals; in many cases the supply of oxygen to the tissues is barely sufficient during rest, and exercise frequently leads to an inadequate supply of oxygen to the tissues and brings on mountain sickness. This occurs less readily, however, in the trained than in the untrained person, since the former uses his muscles more economically, and therefore his demands for oxygen are not so great.

(2) **The Effect of Raised Pressure.**—Men engaged in the building of bridges and tunnels are often compelled to work in caissons, which are filled with compressed air to prevent the inrush of water. They suffer no inconvenience, and the respiratory movements are not affected while they are in the caisson, even though the pressure may be three or four atmospheres. Under this pressure, however, the blood dissolves an increased amount of oxygen and nitrogen, and when a man leaves the caisson, and the pressure to which the blood and tissue fluids are exposed is reduced to one atmosphere, most of the nitrogen, previously in solution, is evolved as bubbles, which may obstruct the flow of blood along the blood-vessels or through the heart.

The symptoms caused by this obstruction, and known as caisson disease, are very varied, and include paralysis, severe abdominal pain, and collapse. The disease is prevented by allowing the man to pass from the caisson into a special air chamber, in which the pressure is gradually lowered to that of the atmosphere so as to prevent any sudden evolution of nitrogen.

CARBON MONOXIDE POISONING.

The affinity of carbon monoxide for hæmoglobin is about 130 times as great as that of oxygen; and when air containing even a small percentage of carbon monoxide is breathed, the oxyhæmoglobin is replaced by carbon monoxide hæmoglobin, and asphyxia is produced. The fatal effects of breathing air containing coal gas, in which carbon monoxide is present, are brought about in this way; but death may often be prevented by the administration of pure oxygen, which not only increases the amount of oxygen dissolved in the blood and carried to the tissues, but, by its mass action, gradually displaces the carbon monoxide from its combination with hæmoglobin.

SECTION VI.

THE INFLUENCE OF THE RESPIRATORY MOVEMENTS ON THE CIRCULATION.

On examining a tracing of the blood pressure, it is often noticed that the pressure shows oscillations corresponding with each respiratory movement, rising a little with each inspiration and falling during expiration. Further, the pulse is more frequent during inspiration and less frequent during expiration (fig. 114). The difference in the pulse rate is due to a slight diminution of the tone of the vagus during inspiration, which allows the heart to beat more rapidly; it is abolished by section of the vagi, but the respiratory oscillations of the blood pressure are not affected by this procedure.

At the end of expiration, the pressure inside the cavity of the chest is slightly below atmospheric pressure and the pressure on the walls of the great veins and of the heart is negative, whereas the pressure in the jugular vein, for example, is slightly higher than that of the atmosphere. Owing to this difference of pressure in the vessels within and outside the chest, blood tends to be sucked along the great veins and into the heart. With each inspiration the negative pressure is increased, and the flow of blood into the heart becomes more rapid. The thin-walled auricles are also slightly dilated by the negative

pressure, and the flow of blood to the heart is thus further assisted, the thick-walled ventricles and arteries being practically unaffected. As the result of the additional blood reaching the heart during inspiration, the amount of blood expelled from the heart at each beat becomes larger, and the arterial pressure rises. Conversely, during expiration the negative pressure diminishes again, less blood is sucked into the heart, its output is smaller, and the arterial pressure falls.

A second factor which conduces to the rise of arterial pressure is the descent of the diaphragm during inspiration; this, by diminishing the size of the abdominal cavity, raises the intra-abdominal pressure and squeezes blood out of the abdomen along the inferior vena cava into the heart.

According to some observers, a third factor also takes a part in producing the rise of blood pressure during inspiration, namely, changes in the size of the vessels forming the capillary network in the lungs. The lung is exposed on its inner surface to atmospheric pressure, and on its outer surface to a pressure which is less than atmospheric pressure. An increase in this difference of pressure, such as occurs during inspiration, will dilate the capillaries in the wall of the lungs, blood will flow through them more rapidly, and a larger quantity will reach the left ventricle in a given time; the additional blood thus reaching and expelled from the left ventricle will raise the arterial pressure. Conversely, during expiration, when the difference of pressure on the two sides of the lung wall diminishes, the capillaries will shrink, blood will flow less rapidly through them into the left ventricle, and the blood pressure will fall. Other writers, however, consider that changes in the calibre of the capillaries play no part in the variations of blood pressure which accompany the respiratory movements; they regard these variations as being due entirely to alterations in the amount of blood which is drawn into the heart by the negative pressure on the walls of the great veins, and is driven out of the abdominal veins by the contraction of the diaphragm.

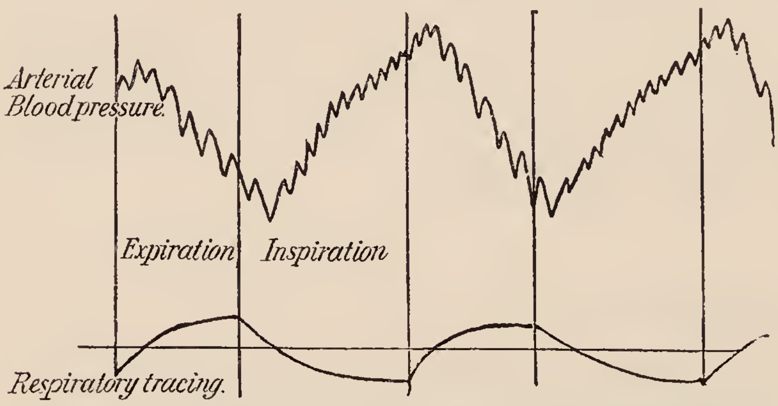


FIG. 114.—Effect of respiratory movements on arterial blood pressure. (Starling's *Principles of Physiology.*)

The negative pressure during inspiration varies with the depth of the inspiration, and, when the breathing is very forcible, the rise and fall of blood pressure during inspiration and expiration may become very

marked. The rise of pressure begins just after the beginning of inspiration, and continues for a short time during expiration, so that the variations in blood pressure are not quite synchronous with the respiratory movements. This delay in the rise of blood pressure is due to the fact that, when more blood enters the right auricle at the beginning of inspiration, it has to travel through the lungs before it reaches the left ventricle and is expelled into the aorta. Again, at the beginning of expiration there is, for the same reason, a slight delay in the diminution in the amount of blood sent out by the left ventricle.

In man the alterations in blood pressure produced by the respiratory movements are of very complex origin, and the effects are not so constant as those just described for animals; they vary with the type of respiration, a costal inspiration causing a fall, and a diaphragmatic inspiration causing a rise of blood pressure.

SECTION VII.

MUSCULAR EXERCISE.

The supply of oxygen to the tissues and the removal of carbonic acid are effected by the conjoint action of the respiratory and circulatory systems; and, in order that the tissues may receive their due supply of oxygen, it is necessary, not only that the blood in its passage through the lungs should become fully saturated, but that an adequate amount of blood should be carried to the tissues. We find, therefore, that the demands of the body as a whole for an increased amount of oxygen are met by alterations in both the respiratory and circulatory systems, and that for this purpose the two systems exert a correlated action, which is very clearly illustrated in muscular exercise. Many of these changes have already been considered, but they may conveniently be summarised here.

During muscular exercise the contracting muscles require a large amount of oxygen and give off much carbonic acid. By means of increased respiratory movements sufficient oxygen reaches the alveolar air to replace that which passes into the blood, and sufficient carbonic acid is removed from the lungs to keep its percentage in the alveolar air almost unchanged; and the blood, during exercise, is almost as fully oxygenated as during rest, the hæmoglobin being at least 90 per cent. saturated with oxygen.

The adjustment of the respiratory mechanism to the increased needs of the muscles is brought about (1) by impulses passing from the cerebral cortex to the respiratory centre at the very outset of exercise,

which increase the sensitiveness of the centre to carbonic acid (p. 275); and (2) by the chemical stimulus of the additional carbonic acid produced in the muscles. In addition, the respiratory centre is stimulated by lactic acid, the amount of which in the blood increases during muscular exercise, if the latter is at all severe. During rest, the blood in man contains only minute traces of lactic acid, and this is not increased by moderate exercise, such as walking, though running for a few minutes raises the amount of lactic acid in the blood, and lactic acid may be detected in the urine. Notwithstanding the great increase in the supply of oxygen to the actively contracting skeletal muscles, the latter are unable to oxidise all the lactic acid which is formed in them in these circumstances. The excess of lactic acid passes into the circulation, and not only stimulates the respiratory centre, but also (p. 258) renders the blood more readily dissociable and enables the muscles to obtain oxygen more easily.

The changes in the circulation during exercise are acceleration of the heart and a rise in the mean arterial pressure, associated with dilatation of the blood-vessels to the muscles. The acceleration of the heart is due primarily to diminution in the tone of the vagus centre and, therefore, of the restraining influence which it normally exerts on the heart. It is seen at the very beginning of exercise, being brought about in all probability by impulses passing from the cerebral cortex to the vagus centre, and is particularly well marked in animals, such as the dog, which are accustomed to take severe exercise. Subsidiary factors which contribute later to the acceleration are (1) an increase in the tone of the accelerator centre, and (2) the setting free of adrenalin into the circulation. At the same time, the increased respiratory movements and the muscular movements increase the amount of blood reaching the heart, and its output becomes larger.

The rise in the arterial blood pressure is due partly to the increased output of the heart, and partly to constriction of the splanchnic vessels; and, since the blood-vessels to the muscles are dilated, the flow of blood is largely diverted from the abdominal organs to the skeletal muscles.

Owing to these factors, the velocity of the blood flow through the lungs, and indeed through the whole body, becomes greater; and within a given time a much larger quantity of oxygen can be taken up by the blood as it passes through the lungs, and can be transported to the tissues, than during rest.

During exercise a large amount of heat is evolved in the muscles, and the temperature of the body may rise to 100° or 101° F.; this rise in temperature tends further to accelerate the heart, and is one of

the reasons why the pulse rate remains rapid for some time after the exercise has come to an end.

Second Wind.—It is a matter of common knowledge that, in a trained person, the respiratory discomfort which occurs soon after the beginning of exercise usually passes off in a few minutes, and the exercise can then be continued for a long period without further inconvenience, the individual being said to have gained his *second wind.* Its causation has been much discussed, and is not fully understood, though it is probably due in part to the fact that a trained person uses his muscles more economically than an untrained person, and therefore produces less carbonic acid. The observation that the tension of carbonic acid in the alveolar air may fall with the onset of second wind suggests that such is the case. If the muscles are used more economically after a brief period of exercise, the decrease in the production of carbonic acid will lessen the stimulus to the respiratory centre, and will account for the absence of panting and respiratory distress in second wind. It is probable that adjustment also takes place in the circulation, since the process of training consists essentially in the better adaptation of the circulatory system to withstand extra strain.

CHAPTER X.

THE DIGESTIVE SYSTEM.

SECTION I.

THE NATURE OF DIGESTION.

The process of digestion consists essentially in the splitting up of the molecules of the food-stuffs into a large number of much smaller molecules which, partly because of their smaller mass, are easily absorbed through the mucous membrane of the digestive tract. Thus the digestion of fat results in the splitting up of the molecule of neutral fat into one molecule of glycerol and three molecules of fatty acid, a single protein molecule is broken up into a very large number, probably a hundred or more, of molecules of amino-acids, while one molecule of starch is subdivided into about two hundred molecules of dextrose. In all cases the process is one of hydrolysis, and in the case of protein and starch it takes place in a series of stages. Similar changes can be brought about by chemical means, such as boiling with mineral acids, but the digestive juices achieve their results more rapidly and effectively, at the temperature of the body, by means of certain active agents known as enzymes or ferments.

ENZYMES.

No enzyme has yet been isolated and analysed, and therefore nothing definite is known as to the composition and constitution of these bodies except that they are not proteins. They exist, however, in great variety in animal and vegetable cells, and they possess very definite properties. (1) They are colloidal substances, and do not diffuse through animal membranes. (2) They only act in solutions, having no effect in the dry state. (3) As a rule each enzyme is specific; it will produce its own definite effect and no other. Thus the ptyalin of saliva converts starch into maltose, but has no action on protein. (4) Enzyme action is markedly affected by temperature. It is most effective, in the case of the enzymes of the animal body, at

37° to 40° C.; and it is destroyed by the temperature of boiling water. (5) Enzymes will act indefinitely if the products of their activity are removed, that is, they are not used up and do not form permanent compounds with the substances on which they exert their activity. In other words, no definite proportion of enzyme to substrate, that is the material acted upon, is necessary; but the greater the proportion of enzyme to substrate the more quickly is the final result attained.

The foregoing characteristics are the principal tests by which an enzyme may be distinguished. But some further points in connection with the origin and action of ferments have to be noted, and help to throw light on the probable mode of action of these bodies. Enzymes are produced in living cells, and they either exert their action on substances present in the cell body, or are turned out of the cell, as in the case of the digestive juices, to exercise their function elsewhere. That function is to be regarded as the acceleration of a process which tends to go on, it may be with infinite slowness, in the absence of an enzyme. The enzyme may be compared with the grease on the slip-ways when a ship is launched, in that by its presence it facilitates a process brought about by quite independent forces. The particular process expedited by the presence of an enzyme is generally that of hydrolysis, in which a large molecule takes up water and then the resulting compound splits into smaller molecules. But in the case of many, if not of all, enzymes, this process may be *reversed*, the smaller molecules being condensed again with the loss of water. For example, the enzyme maltase, if added to a solution of maltose, will convert most of this sugar into dextrose. But if the same ferment is added to a solution of dextrose it will convert a certain proportion of the latter into maltose. The action of maltase is, in fact, to bring about a certain definite proportion between the maltose and dextrose in solution, the proportion, or, as it is called, the *equilibrium point*, varying with the concentration of the solution. Thus maltase, acting upon maltose, might convert it entirely into dextrose if the latter substance were removed at the same rate as it was produced; or, on the other hand, the same enzyme, acting upon dextrose, might convert the latter entirely into maltose, provided the maltose were being simultaneously removed. This reversible enzyme action is of great importance in the body, where, for example, dextrose is at one time converted into glycogen by a synthetic process, while later the glycogen is once more turned into dextrose by a process of hydrolysis.

Enzymes, then, are bodies of unknown constitution, which facilitate certain chemical reactions without providing any energy for these reactions and without being used up in the process. They are, in fact,

organic catalysts, and some suggestions as to their mode of action may be obtained from the study of the methods by which the simpler inorganic catalysts produce their effects. Two examples of the latter may be taken: (1) the effect of spongy platinum in bringing about the combination of hydrogen and oxygen to form water, and (2) the oxidation of indefinite quantities of SO_2 to form SO_3 by the intermediation of nitrogen peroxide. The platinum acts as a catalyst because of its physical properties. Its low surface tension leads to a concentration of the gases at its surface, whereby the molecules are brought into close contact and their chemical interaction is favoured. With this may be compared the first stage in the action of an enzyme, in which a physical union takes place between enzyme and substrate by the process known as *adsorption.*

The nitrogen peroxide, on the other hand, forms an intermediate chemical compound. After yielding part of its oxygen to oxidise SO_2, and thus becoming reduced to nitric oxide, the latter substance takes up oxygen from the air to form nitrogen peroxide once more, and so the process is repeated indefinitely.

$$SO_2 + NO_2 = SO_3 + NO$$
$$NO + O = NO_2.$$

The enzymes known as oxidases possibly act in a somewhat similar way to the nitrogen peroxide in this reaction. Many oxidases are believed to consist of an organic peroxide combined with a peroxidase. The latter splits off oxygen from the peroxide, which again takes up oxygen, and the process is repeated. In the case of enzymes it is found that, with a limited amount of ferment, the same amount of substrate is acted upon in a given time whether the observation is made early or late in the process. It would, therefore, appear that the mode of action of the organic catalyst is comparable with that of the inorganic catalyst which acts chemically, the enzyme probably being adsorbed by the substrate, which is then capable of taking up water and splitting up, with the result that the enzyme is once again set free.

In the case of most enzyme reactions the velocity of the process tends to diminish after it has gone on for a time. An enzyme has not only a specific affinity for its particular substrate, but it may also have an affinity for the products of the reaction, and by forming combinations with these it may be put out of action. By-products are also formed in some enzyme reactions, and these, for example acids or alkalies, may either increase or decrease the power of the enzyme itself and so modify the rate of the process. In some cases these by-products destroy the enzyme and so bring the reaction to an end.

THE STAGES OF DIGESTION.

The activities of the digestive tract are two in number. First, there is a motor mechanism by means of which the contents of the tract are moved progressively from mouth to œsophagus, stomach, small intestine, and large intestine, and are finally expelled. Secondly, there is a series of secretory glands, which produce the digestive juices met with in the different regions of the tract. These juices have no effect on water and inorganic salts, but their enzymes bring about hydrolytic changes in the protein, carbohydrate, and fatty constituents of the various food-stuffs. Food is mixed with saliva in the mouth and is then quickly passed on to the stomach, in which it remains for some time. During the early part of its stay in the stomach, the starch of the food undergoes the preliminary stages of digestion through the agency of the saliva. Gastric juice is also secreted, and originates digestive changes in the proteins and, to a certain extent, in the fats, while it gradually destroys the salivary enzyme.

The next stage consists in the forwarding of the stomach contents into the small intestine, where the pancreatic juice and bile carry the digestive changes in the carbohydrates and proteins a stage further, and complete the digestion of the fats.

Finally, the intestinal juice effects the concluding stages of carbohydrate and protein digestion, and the hydrolytic products of carbohydrates, proteins, and fats, together with inorganic salts and water, are absorbed through the wall of the small intestine. Undigested substances and certain waste matters reach the large intestine, where much of the remaining water is absorbed, the residue constituting the fæces. Under normal conditions, such of the constituents of a meal as are not absorbed begin to reach the large intestine four to five hours after the ingestion of the meal, and the residues are finally expelled from twelve to twenty hours later, so that all the processes described above are going on simultaneously, there being as a rule an interval of not more than four or five hours between meals during the day.

SECTION II.

CHANGES IN THE FOOD IN THE MOUTH.

The changes which take place in the food in the mouth are chiefly mechanical, its stay in this region being so brief that the saliva has not time to produce an appreciable chemical effect. Salivary digestion takes place mainly in the stomach in the interval before the enzyme is destroyed by the gastric juice. In the mouth the food is masticated, that is, it is broken up and formed into a pulpy mass by the vertical,

lateral, and antero-posterior movements of the jaws, the various fragments being directed in turn by the muscular movements of the cheeks, lips, and tongue, so that they come between the opposing teeth. At the same time, saliva is being poured out in considerable quantity, and is being intimately mixed with the food by the same grinding process. After mastication the insalivated food is collected into a bolus on the tongue by further movements of the cheeks, lips, and tongue itself, and in this condition it is ready for the process of swallowing.

The Composition of Saliva.—Saliva, which is the mixed secretion of the parotid, submaxillary, and sublingual glands, together with that of the buccal glands scattered about the mucous membrane of the mouth, is a viscid, colourless, cloudy fluid, with a slightly alkaline reaction, and an average specific gravity of about 1005. It contains as a rule over 99 per cent. of water and less than 1 per cent. of solid constituents. The latter consist of coagulable proteins, mucin, a diastatic enzyme called ptyalin, and inorganic salts. Calcium salts are present in considerable proportion, and are responsible for the formation of tartar on the teeth. Traces of potassium thiocyanate are often present, and may be recognised by the red colour which they give with ferric chloride. The viscidity of saliva is due to the mucin it contains; the cloudiness is the result of the presence of numerous squamous epithelial cells from the mucous membrane of the mouth, and of the so-called salivary corpuscles. The latter are granular spherical cells resembling leucocytes, some of which are probably derived from the lymphoid tissue of the tonsils, while others may come from the salivary glands themselves.

The Functions of Saliva.—The saliva serves other purposes besides that of digestion, and in the dog it serves other purposes only, there being no ptyalin in the saliva of that animal. By its admixture with the food it facilitates mastication and deglutition. By keeping the lips and tongue moist, it is of service in those movements which are essential to the function of speech; and, by dissolving substances which affect the sense of taste, it renders these capable of stimulating the gustatory end-organs.

In these cases the use of saliva is a mechanical one, whereas in its digestive function it gives rise to chemical change. Ptyalin acts upon starch, converting it into dextrin and maltose. Raw starch is not acted upon by saliva, which cannot dissolve the cellulose capsules of the starch granules, and to enable ptyalin to produce its effect upon starchy foods, these must be boiled or otherwise cooked. When starch granules are heated in the presence of water, they swell, and the cellulose capsules are ruptured so that the starch passes into a pseudo-solution.

If a little saliva is mixed with some boiled starch paste in a test-

tube and the mixture kept at 40° C., the changes which occur may be conveniently observed. The original starch solution is slightly opalescent. Within a few seconds it becomes clear, but if a drop of the clear solution be added to a drop of dilute iodine a blue colour results, as in the case of starch which has undergone no digestive change. This, the first stage in the process, is that of soluble starch. A little later, a drop of the fluid gives a purple colour with iodine, later still a reddish brown, and finally an "achromic point" is reached, that is, a stage when the digest does not give a colour reaction with iodine. The digestive power of any particular saliva can be estimated by the time taken to reach the achromic point.

The purple and reddish brown reactions with iodine indicate the presence of erythrodextrin, at first mixed with a certain amount of unaltered starch so that the dextrin reaction is complicated by the blue starch reaction, but later without any such admixture. If, at any time after the indications of the presence of dextrin appear, a little of the solution be boiled with an alkaline solution of cupric sulphate, reduction of the latter will take place, a precipitate of yellow cuprous oxide being formed. This reaction indicates the presence of a reducing sugar, maltose. In the achromic stage the solution is found to contain maltose and a form of dextrin, which gives no colour reaction with iodine and is therefore called achroo-dextrin. The ultimate result of the digestion usually consists of about 80 per cent. of maltose and 20 per cent. of achroo-dextrin, and although the proportion of the latter may be reduced in favourable circumstances to 5 per cent., the conversion of starch into maltose by ptyalin is never complete.

The salivary digestion of starch consists in the taking up of water by the starch molecule, and for each molecule of water taken up a molecule of maltose is split off. In this way the original molecule becomes progressively smaller, and passes through a series of dextrins which are grouped as erythro- and achroo-dextrins according to their reaction with iodine, finally reaching the stage of maltose and achroo-dextrin, on which ptyalin has no further action. The process may be diagrammatically shown thus:—

Starch.

Soluble starch.

Erythro-dextrins Maltose.

Achroo-dextrins Maltose.

Or it may be epitomised in the formula

$$\underset{\text{Starch}}{(C_{12}H_{20}O_{10})_{100}} + 80H_2O = \underset{\text{Maltose}}{80C_{12}H_{22}O_{11}} + \underset{\text{Achroo-dextrin.}}{(C_{12}H_{20}O_{10})_{20}}.$$

Evans' method of determining the amylolytic power of saliva is based upon a calculation of the amount of maltose formed from a given quantity of starch in a definite time. 5 c.c. of mixed saliva are diluted to 50 c.c. with distilled water, and the mixture is filtered. 3 c.c. of the diluted saliva are added to 50 c.c. of a 3 per cent. solution of neutral soluble starch, which is at a temperature of 46° C. Digestion is allowed to proceed at 46° C. for ten minutes, and is then stopped by the addition of a little sodium hydrate. The copper-reducing power is then determined, and the amount of maltose formed is calculated.

The digestive action of ptyalin on starch is most energetic in a neutral medium. Hence it is favoured by the addition of a trace of acid to normal alkaline saliva. Like other ferment processes, it is arrested by a high temperature, and ptyalin itself is destroyed by the slightest excess of hydrochloric acid, even less than is contained in gastric juice. The optimum temperature for the action of ptyalin is 46° C. When a meal is taken, it forms a fairly compact mass in the stomach, but is gradually penetrated by the gastric juice; as this penetration takes place, the ptyalin is gradually destroyed, but about half an hour elapses before salivary digestion in the centre of the mass is finally terminated.

THE SECRETION OF SALIVA.

There is a constant production of saliva in sufficient quantity to keep the buccal mucous membrane moist, but in certain circumstances the flow is largely increased. The conditions which are followed by more profuse production of saliva are (1) the presence of food in the mouth, and (2) the sight, smell, or thought of food. Food in the mouth is followed so promptly by the increased salivary flow that it must necessarily produce its effect through the nervous system. The second group of conditions likewise obviously produce their effect by means of a nervous mechanism. It is clear, therefore, that the secretion of saliva is brought about by a reflex mechanism, the afferent nerves usually being those connected with the buccal mucous membrane, and the efferent nerves those passing to the various salivary glands.

Each salivary gland has a double nerve supply. The chorda tympani nerve is distributed to the submaxillary and sublingual glands (fig. 115), and the parotid receives a branch from the auriculo-temporal nerve. In addition, each gland receives fibres from the sympathetic system. If a cannula is placed in the duct of the submaxillary gland and the chorda tympani is divided, no flow of saliva is observed. But

if the distal portion of the nerve be stimulated, a profuse flow of saliva follows within two or three seconds, while at the same time the blood-vessels of the gland are dilated, and the output of carbonic acid and the intake of oxygen are both increased. Section of the sympathetic fibres is likewise followed by a negative result, while stimulation of the distal portion in the dog leads to the production of a very small flow of viscid saliva, accompanied by constriction of the blood-vessels. In view of these experiments it might appear that the primary effect of the stimulation of the chorda tympani was the dilatation of the vessels, and that the flow of saliva was due to filtration.

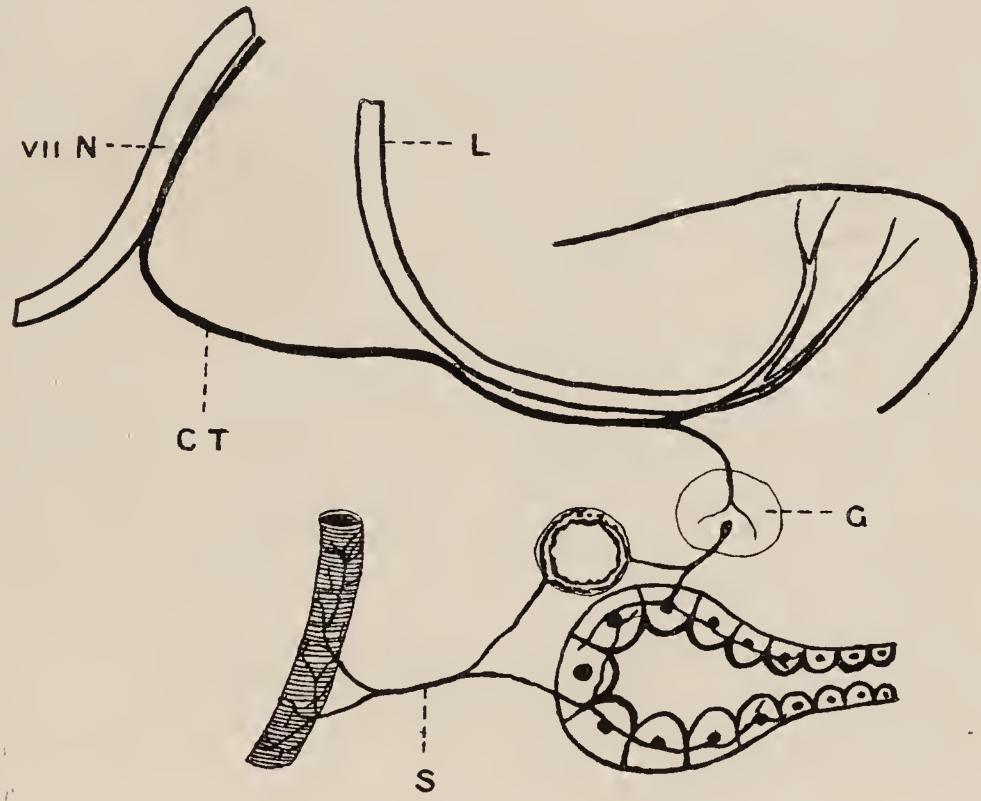


FIG. 115.—Scheme of nerve supply of submaxillary gland.

VII N, facial nerve; C.T., chorda tympani; L, lingual nerve; G, Langley's ganglion; S, sympathetic fibres to the gland.

Filtration is a purely physical process in which fluids pass through a permeable membrane under the influence of pressure. In the process of secretion, on the other hand, work is done by cells; these take up material from the lymph which bathes them and is derived from the blood, effect chemical changes in that material, and discharge the resulting products in the form of a "secretion." In the case of the salivary glands, several facts indicate that the process is a secretory one. (1) The cells of the salivary gland, as will be described more fully later, accumulate granules during the period when saliva is not being poured out, and discharge them during the period of activity. (2) The consumption of oxygen by a salivary gland is increased during the production of saliva, indicating that work is being done. (3) Two of the constituents of saliva, mucin and ptyalin, do not exist in the

blood, and must be formed in the gland. (4) The pressure in the duct of the gland during activity may be greater than the pressure in the carotid artery, and therefore much greater than that in the capillaries of the gland. (5) The molecular concentration of saliva in inorganic salts is only about half that of blood, whereas if saliva were a filtrate the concentration of salts would be the same as that of blood. (6) Secretion may be obtained in the absence of blood. If the head of a

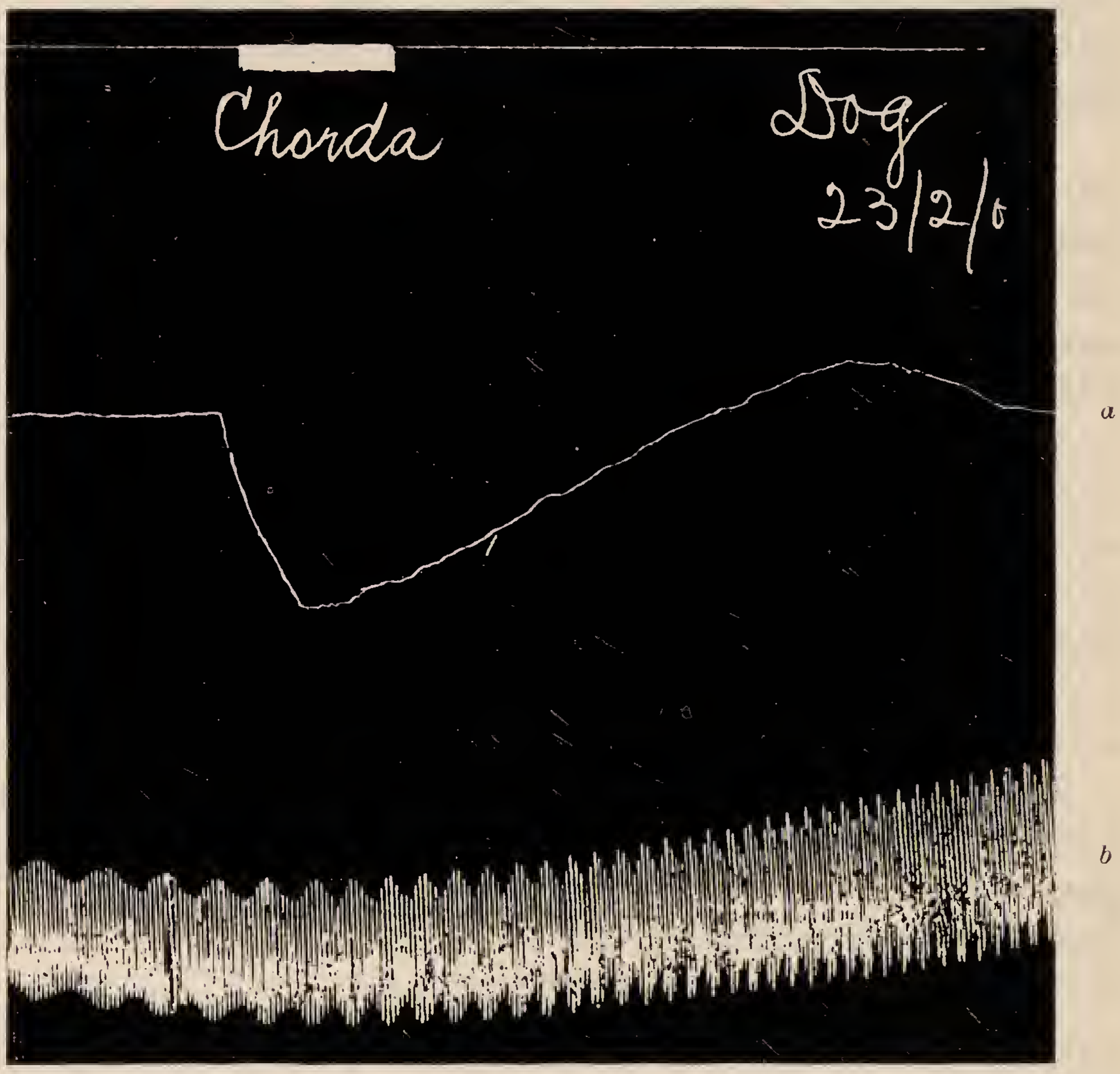


Fig. 116.—Effect of stimulation of the chorda tympani on the volume of the submaxillary gland. (Bunch.)

a, volume of gland ; *b*, blood pressure.

rabbit be cut off and the chorda stimulated immediately, a flow of saliva is obtained. (7) The blood-vessels may be dilated without any secretion taking place. In an animal to which atropine has been administered stimulation of the chorda is followed by no secretion of saliva, although the vessels become fully dilated.

It has been suggested that, whereas the nervous factor undoubtedly originates the salivary flow, other factors come into play to assist in its continuance. Stimulation of the chorda is followed by a temporary diminution in the volume of the gland, although the blood-vessels are

dilated (fig. 116). This shrinkage must be due to the first discharge of material from the secretory cells. As a result of the loss of fluid of lower molecular concentration, the osmotic pressure in the cells themselves is raised and water is attracted to them from the lymph. In this way the molecular concentration of the lymph is also increased, and therefore water is attracted from the blood. Moreover, as the result of the secretory activity of the cells, large molecules are being split up into a large number of smaller molecules, and the discharge of these metabolites into the lymph tends still further to raise the osmotic pressure and ultimately the amount of that fluid.

If the chorda tympani has been divided, a flow of watery saliva begins from one to three days later, and continues for five or six weeks (paralytic secretion), when the gland atrophies and the secretion ceases. If the chorda of one side only has been divided, a similar secretion is said to take place in the opposite gland, an *antiparalytic* secretion, the explanation of which is not clear.

Division and stimulation of the nerves to the parotid and sublingual glands give parallel results to those described above for the submaxillary gland.

The physiological centre for the reflex mechanism of salivary secretion is situated in the medulla oblongata. The cranial efferent fibres take origin in the nucleus of the nervus intermedius. Those for the submaxillary and sublingual glands join the facial nerve and leave it in the chorda tympani, which subsequently joins the lingual branch of the fifth nerve. The fibres for the parotid join the trunk of the glossopharyngeal nerve, and, leaving it by its tympanic branch, reach their destination after passing through the tympanic plexus, the Vidian nerve, the otic ganglion, the second division of the fifth, and the auriculotemporal nerve. The cranial fibres for the salivary glands belong to the autonomic nervous system, and in the case of the submaxillary and sublingual glands the post-ganglionic fibres take origin in Langley's ganglion and the submaxillary ganglion respectively. This can be proved by painting these ganglia with nicotine, after which stimulation of the chorda tympani is without effect on the glands.

The pre-ganglionic fibres of the sympathetic nerves to the salivary glands pass down the spinal cord, leaving it by the anterior roots of the upper three thoracic nerves to join the sympathetic chain. They run in the cervical sympathetic nerve up to the superior cervical ganglion, where the post-ganglionic fibres arise. These pass on the walls of the external carotid artery to the various glands.

THE CHANGES WHICH ACCOMPANY SECRETION IN THE SALIVARY GLANDS.

(1) It has already been pointed out that a temporary diminution in the volume of the gland follows stimulation of the secretory nerve. This is followed by an expansion due to the dilatation of the blood-vessels. Further, secretion is accompanied by histological changes and by an alteration in electrical potential.

(2) Histologically the salivary glands are of two types—serous glands, which produce a fluid containing proteins and ptyalin, and mucous glands, the secretion of which contains mucin. The salivary glands of the dog, however, secrete no ptyalin. The parotid in man and most animals belongs to the serous type; the submaxillary and sublingual are generally mucous, but the former is serous in the rabbit and mixed in man. The general structure of a salivary gland is of the compound acinous type, each acinus being lined by columnar or cubical cells, and the whole being held together by connective tissue.

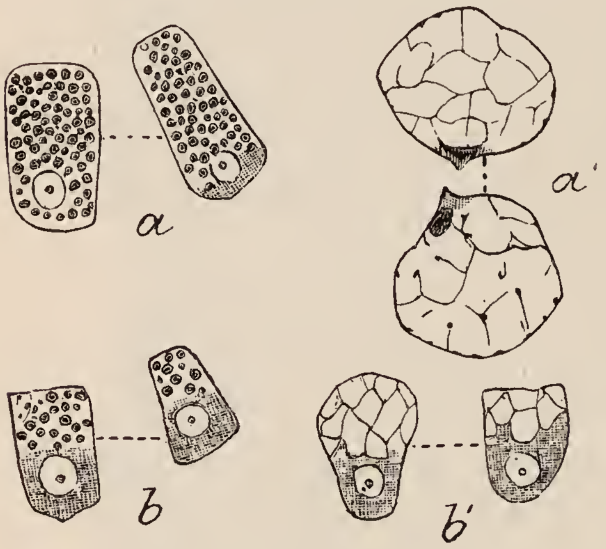


Fig. 117.—Mucous cells from fresh submaxillary glands of the dog. (Langley.) From Schäfer's *Essentials of Histology*.

a, from a resting or loaded gland; *b*, from a gland which has been secreting for some time; *a'*, *b'*, similar cells which have been treated with dilute acid.

If a portion of a mucous gland, which is in the resting condition, be teased in 2 per cent. salt solution, the individual cells are seen to be somewhat columnar in shape and to be filled with large granules which swell up and disintegrate on the addition of acetic acid. If the gland be hardened in alcohol and stained sections be examined, no granules are visible, but the body of the cell is clear, with a delicate network, and the nucleus is flat and lies at the base of the cell. In the case of a gland which has been made to secrete profusely, either by means of electrical stimulation or by the administration of pilocarpine, the granules are fewer in number and are found in the part of the cell which abuts on the lumen of the acinus; and the cell is smaller than that in the resting condition (fig. 117). The hardened specimen shows a larger proportion of protoplasm, and the nucleus does not lie so close to the base of the cell. In the process of secretion, therefore, there has been a discharge of the granules contained in the cell. But from their behaviour to reagents it is clear that the granules do not represent the

final stages of the secretory process, for mucin itself is precipitated by acetic acid. The material contained in the granules must be a precursor of mucin, and it has therefore been called mucinogen.

The cells of the serous type, treated in the same way, are more cubical in shape, with a central nucleus, and in the resting state are diffusely filled with much finer granules, which, as they are supposed to consist of a precursor of ptyalin, have been called zymogenic. As in the case of the mucous gland, the serous cell becomes smaller during activity and the granules are diminished in number, especially towards the base of the cell (fig. 118). In sections of the hardened gland which have been stained, the cells even in the resting stage always appear to contain a relatively greater amount of protoplasm than the mucous cells.

In both mucous and serous cells the formation of granules is pre-

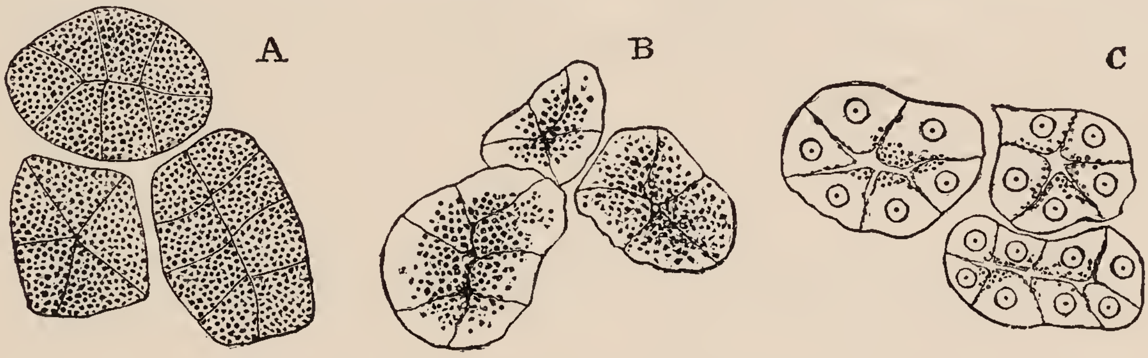


FIG. 118.—Alveoli of a serous gland. (Langley.) From Schäfer's *Essentials of Histology*.

A, at rest. B, after a short period of activity. C, after a prolonged period of activity. In A and B the nuclei are obscured by the granules of zymogen.

ceded by the appearance of filaments, basophile in character, which have received the general name of *ergastoplasm*.

(3) In the resting condition of a salivary gland an electrical current can be detected by the capillary galvanometer, the direction of which in the gland is from the acini towards the duct. This current, in the case of the submaxillary gland, undergoes a diphasic variation on stimulation of the chorda tympani, becoming first increased in intensity and then reversed in direction. Stimulation of the sympathetic nerve is followed by a negative variation only.

DEGLUTITION.

The bolus of food formed in the mouth is conveyed through the pharynx and œsophagus into the stomach by the act of deglutition, which originates as a voluntary process and is continued by nervous reflexes. In the first or voluntary stage the jaws are closed and the tongue is raised so as to press against the palate, the latter movement being due to contraction of the mylohyoid aided by the intrinsic muscles of the tongue itself. At the same time the base of the tongue is drawn

slightly backwards by the contraction of the stylo-glossi and palato-glossi. In this way the bolus is propelled through the opening bounded by the anterior pillars of the fauces, beyond which the act becomes involuntary. The later stages are subdivided anatomically into pharyngeal and œsophageal, but physiologically they are to be looked upon as a continuous series of reflexes.

While the bolus is in the pharynx, the soft palate is raised so as to form an inclined plane and prevent the passage of food into the nares. At the same time the opening into the respiratory tract is guarded by the elevation of the larynx under the posterior end of the retracted tongue, by the constriction of the aperture of the larynx itself, and by closure of the glottis. The arytenoid cartilages are rotated inwards by contraction of the lateral crico-arytenoid muscles, and approximated by contraction of the arytenoideus. They are at the same time drawn forward by contraction of the thyro-arytenoids, so that the glottis takes the form of a **T**-shaped slit. The opening of the larynx is diminished in size by contraction of the ary-epiglottidean muscle fibres. At the same time, by the elevation of the larynx and the drawing back of the tongue the opening is further guarded by the lower part of the epiglottis.

The passage of the bolus through the œsophagus is effected by a wave of contraction preceded by relaxation in the muscular wall of the tube. The œsophagus consists of four coats: (1) a mucous coat, bounded externally by a layer of smooth muscle fibres arranged longitudinally, the *muscularis mucosæ*, and lined by stratified squamous epithelium; (2) a submucous coat of loose connective tissue containing mucous glands, which supply a lubricating fluid; (3) a muscular coat, composed of striated muscle in the upper part of the tube and of smooth muscle in the lower part, and consisting of an outer longitudinal and inner circular layer; and (4) a fibrous coat. Owing to the more rapid contraction of the striated muscular fibres, the bolus travels more quickly in the upper part of the œsophagus than in the lower part.

The time taken by the act of deglutition is normally five or six seconds. This may be ascertained by listening over the pharynx or the œsophagus by means of a stethoscope, the entrance of the food into the pharynx at the beginning of the act, and again into the stomach at its close, being characterised by distinct sounds. A more precise method is direct observation with the aid of Röntgen rays, the food swallowed in this case being mixed with bismuth so that it gives a well-marked shadow.

During swallowing there is temporary inhibition of respiratory movements, and in this way a further safeguard is introduced against the entrance of food particles into the larynx.

The nerves chiefly concerned in the first stage of deglutition are the fifth cranial nerve to the muscles which close the jaws and the mylohyoid, and the twelfth nerve to the muscles of the tongue. The afferent nerves connected with the reflex act are the second division of the fifth, the glosso-pharyngeal, and the branches of the superior laryngeal nerve to the pharynx. The efferent nerves are those which form the pharyngeal and œsophageal plexuses, the ninth, tenth, and eleventh cranial nerves. The reflex centre is in the medulla oblongata, and it appears to consist of a series of centres; for if the œsophagus be cut across, stimulation of the afferent nerves will be followed by an orderly wave of contraction, just as in the intact œsophagus.

The inhibition of respiration which accompanies swallowing depends on stimulation of the glosso-pharyngeal nerve; if the latter is divided and the central portion is excited electrically, the respiratory movements are arrested for a period corresponding with that of a normal act of deglutition, that is, for five or six seconds.

SECTION III.

THE STOMACH AND ITS FUNCTIONS.

The stomach forms a dilated portion of the digestive tube capable of storing considerable quantities of nutritive material, and it thus obviates the necessity of taking food at inconveniently frequent intervals. The food remains in the stomach for some hours, and during this period it is acted upon by the gastric juice, so that, when it afterwards comes under the influence of the more potent digestive juices found in the small intestine, the hydrolysis of the protein constituents is already well advanced, some of the fats have been acted upon, and, as has already been described, the saliva has effected a conversion of starch into dextrin and maltose.

The Composition of Gastric Juice.—Gastric juice may be obtained for analysis by producing a permanent gastric fistula in an animal. Pawlow's method is to make an incision in the stomach, separating it into a larger and a smaller portion. The larger portion is stitched up and remains in continuity with the digestive tract. The smaller portion is kept separate from the larger by a layer of mucous membrane, and is made to open on the surface of the body (fig. 119).[1] It is found by experiment that the juice secreted by the small stomach has the same composition as that produced by the large stomach, and also that it is secreted in the same proportional amount when the available extent

[1] We are indebted to the kindness of C. Griffin & Co., Ltd., for permission to use these diagrams.

of mucous membrane is taken into consideration; moreover, it has the advantage of being free from admixture with food.

The juice obtained in this way is a clear fluid having a specific gravity of 1003–5 and an acid reaction. It consists of about 99 per cent. of water and 1 per cent. of solids, the latter including mucin, proteins, enzymes, and inorganic salts. The juice also contains free hydrochloric acid in the proportion of about 0·2 per cent. in man; the percentage is

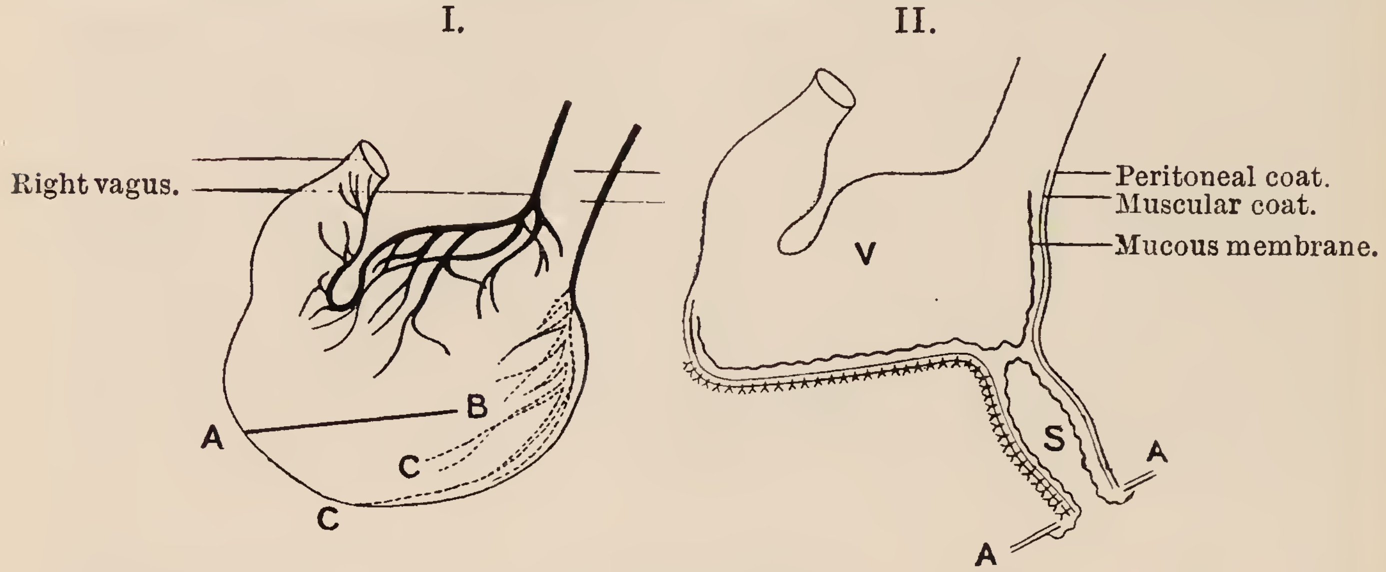


FIG. 119.—Pawlow's method of forming a subsidiary stomach. (From Pawlow's *Work of the Digestive Glands.*)
I., first stage: A—B, incision. II., lesser stomach completed: S, lesser stomach; A, abdominal wall.

rather higher in the dog and other carnivorous animals. The salts are chiefly chlorides and phosphates of potassium, sodium, calcium, and magnesium, the base in largest proportion being potassium.

The existence of free hydrochloric acid may be proved by two tests: (1) A solution of Congo red added to gastric juice gives a blue colour, showing the presence of free mineral acid. (2) If a drop of Gunzberg's reagent (phloroglucin-vanillin) be evaporated to dryness and a drop of gastric juice be added to the residue and gently heated, as drying takes place a bright red colour is developed, proving that the acid is hydrochloric.

THE FUNCTIONS OF THE GASTRIC JUICE.

It has already been pointed out that the acid of the gastric juice destroys the ptyalin of the saliva, but the hydrolysis of the carbohydrates of the food may be continued, to some extent at least, by the hydrochloric acid in the stomach. This chemical hydrolysis, however, if it occurs, is of less importance than the action of the gastric enzymes upon proteins, milk, and fats.

The digestive action of gastric juice can be studied, like that of saliva, by means of experiments in test tubes. Fresh gastric juice obtained from a fistula may be used, but it is generally more convenient to make an artificial extract. For this purpose the mucous membrane of a pig's stomach is cut in small pieces and extracted

with glycerol. By adding some of the glycerol extract to 0·2 per cent. hydrochloric acid an artificial gastric juice is obtained.

(1) If a few flakes of fibrin be placed in a test tube containing such an artificial juice and the tube be kept at a temperature of 37° C., it will be observed that the fibrin gradually swells up and then dissolves. If the solution is neutralised, a precipitate of acid metaprotein is formed. If this is removed by filtration and the filtrate is boiled, a coagulum of soluble globulin may be formed. When this is removed by filtration, the solution gives a pink colour on the addition of dilute copper sulphate and caustic soda, owing to the presence of proteoses and peptones.

Further analysis of this filtrate shows that several varieties of proteose and at least two kinds of peptone are present. The proteoses are classified as primary and secondary, the primary group being precipitated by the addition of an equal volume of saturated solution of ammonium sulphate; when this precipitate has been removed by filtration, the secondary varieties are precipitated by full saturation with the same salt. When the latter precipitate is removed, the solution contains peptones only, although, if the digestion be prolonged for several days, some amino-acids may be present.

The changes produced in the fibrin are due to the activity of an enzyme, *pepsin*, which in the presence of dilute hydrochloric acid brings about hydrolysis of the protein molecule and breaks it up into smaller and more soluble molecules. The first change produced is the solution of the fibrin with the production of a substance known as soluble globulin. This is then changed into acid metaprotein, and, by successive hydrolytic stages, the various proteoses, and finally peptones, are formed. Digestion in the stomach never passes beyond the peptone stage, and in fact the conversion into peptone is not complete when the contents of the stomach are passed on into the small intestine.

The stages of peptic digestion of protein may be represented in tabular form thus—

$$\begin{array}{c}\text{Protein}\\ \downarrow\\ \text{Soluble globulin}\\ \downarrow\\ \text{Acid metaprotein}\\ \downarrow\\ \text{Primary proteoses}\\ \downarrow\\ \text{Secondary proteoses}\\ \downarrow\\ \text{Peptones}\end{array}$$

Some proteins which occur in food do not undergo these changes. Thus *elastin* is unaffected by peptic digestion in the time available in

the stomach. The *collagen* of connective tissue is probably converted first into gelatine and then into gelatoses and gelatine peptones. The protein constituent of the conjugated proteins is usually converted into proteose and peptone, the prosthetic group being set free. Thus in the digestion of *nucleo-protein* by gastric juice an insoluble residue of nuclein is formed; in the digestion of *mucin* (gluco-protein) glucosamine is found in the products.

(2) The effect of gastric juice upon *caseinogen*, the phospho-protein of milk, is peculiar in that there is a conversion of the caseinogen into a comparatively insoluble substance, casein. This action of gastric juice has been for many years ascribed to a separate ferment called *rennin*, but latterly evidence has been brought forward which suggests that the formation of casein from caseinogen is due to pepsin itself. The matter has not been conclusively settled, and it will be convenient to retain the term rennin in the meantime when describing the effect of gastric juice on caseinogen.

The action of rennin can be demonstrated by adding a little of an extract containing this enzyme to a quantity of milk and allowing the mixture to stand for a time at a temperature of 37° C. In a few minutes the milk becomes clotted, and after a time the clot shrinks, squeezing out a clear fluid, whey, which contains all the constituents of milk except caseinogen and fat. It can be shown that the fat is entangled in the clot in an unaltered form, so that the coagulation is brought about by the action of the rennin on the caseinogen. If a little potassium oxalate is added to milk, the subsequent addition of rennin does not result in the formation of a clot, but if calcium chloride be added clotting occurs.

Three factors are necessary for the formation of the clot, namely, caseinogen, rennin, and lime salts. If rennin is added to a solution of pure caseinogen, and the mixture is kept for a short time at a temperature of 37° C. and then boiled to kill the enzyme, the addition of calcium chloride will bring about the formation of casein. Obviously the enzyme has produced some change in the caseinogen, and the only factor required to complete the conversion into casein is the addition of lime salts. There is in the first place, therefore, a conversion of caseinogen into "soluble casein" by the action of the enzyme, and secondly, soluble casein combines with lime salts with the production of insoluble casein. The process may be represented thus:—

Caseinogen ← Rennin (or pepsin)
↓
Soluble casein + Calcium salts
↓
Casein

(3) Gastric juice also acts upon neutral fats, but only on those which are in the form of a fine emulsion, such as yolk of egg or milk. The fats are split into glycerol and fatty acids by the agency of an enzyme, *lipase.* The fat-splitting function of gastric juice, however, is limited in extent, and is of relatively small importance as compared with that which takes place in the small intestine. Pepsin indirectly assists the digestion of fat by dissolving the cell envelopes of the fat cells of adipose tissue contained in food. In this way fat is set free and prepared for the subsequent digestive action of pancreatic lipase.

THE SECRETION OF GASTRIC JUICE.

The mechanism of the secretion of the gastric juice is studied by the subdivision of the stomach in an animal in the manner already described (p. 301), the larger part remaining in continuity with the digestive tract, while the smaller subdivision opens freely on the surface of the body. In such an animal, it has been shown that secretion of juice in the large stomach is accompanied by a proportional secretion of juice in the small stomach, and, further, that the two juices are equal in digestive power.

The secretion of gastric juice begins about five minutes after an ordinary meal is taken, and continues steadily during the period of digestion of the stomach contents. The initial secretion has been shown to be produced by a nervous mechanism, this being supplemented, after a variable time, usually twenty to forty-five minutes, by a further flow excited by a chemical stimulus.

The Nervous Mechanism of Gastric Secretion.—The normal stimulus which excites the flow of gastric juice is the presence of food in the mouth. If the œsophagus of a dog is divided and the two ends are brought to the surface and fixed there, food may be masticated and swallowed by the animal, but none will reach the stomach. In such a case the food which is eaten all escapes by the œsophageal fistula, and is spoken of as a sham meal. In an animal provided with both œsophageal and gastric fistulæ, sham feeding is followed by the secretion of gastric juice, at the same time and in the same way as if the food reached the stomach. This fact points to the probability that the first secretion is due to a nervous reflex, a presumption which is further supported by the observation that, as in the case of the saliva, even the sight or suggestion of food is followed by the appearance of gastric juice. The nervous nature of the stimulus is proved by the effect of division of both vagus nerves to the stomach, after which no secretion takes place on sham feeding or on showing food to the animal. Further proof is

obtained by the production of secretion as a result of stimulation of the vagus. The nerve is divided in the neck, and, four days later, when the cardio-inhibitory fibres have degenerated, the distal end of the nerve is stimulated by a tetanising electric current. Five minutes after the commencement of stimulation, the gastric juice begins to flow.

The efferent nerves concerned in the secretion are therefore the two vagi; the afferent nerves are normally the branches of the fifth and glosso-pharyngeal to the mucous membrane of the mouth, but stimulation of other sensory nerves, such as those of sight and smell, may also excite the secretion. The production of gastric juice through the latter mechanism is spoken of as "psychic" secretion; and the juice formed is described as "appetite juice," since the sight of food in a hungry animal gives rise to its secretion.

The Chemical Factor in the Secretion of Gastric Juice.—In a dog provided with a gastric fistula of the kind described above, a fistulous opening is made into the main stomach, and the two vagi of the animal are divided so as to preclude the possibility of reflex secretion through these nerves. It is then found that the introduction of meat into the main stomach is followed in from twenty to forty-five minutes by a flow of gastric juice. The same effect is produced by Liebig's extract of meat, certain preparations of peptone, or semi-digested bread, but not by pure proteose or peptone, or by bread, starch, or white of egg. Mechanical stimulation, or the introduction of a mechanical irritant, such as sand, is also without effect. The substances which stimulate secretion are spoken of as secretogogues, and Edkins has shown that they produce their effect by exciting the cells of the gastric mucous membrane to produce a hormone. If the pyloric mucous membrane of the stomach is boiled with water or dilute acid, a decoction is obtained, which, when injected into the blood stream, excites the secretion of gastric juice. Extracts of the mucous membrane of the body of the stomach have no such effect. As the result of his experiments, Edkins concludes that the partially digested food products excite the formation of a hormone in the cells of the mucous membrane of the pyloric portion of the stomach; it is called gastric secretin or *gastrin*, and is absorbed into the blood stream, and is carried in the course of the circulation to the glands of the stomach, stimulating them to produce their secretion.

The group of *hormones*, to which gastrin belongs, possess certain definite properties. They are substances of relatively low molecular weight, and are easily diffusible. Each exercises a specific function in exciting the activity of a particular organ or tissue, and, when its

function is performed, it is rapidly destroyed in the body. It does not act as an antigen, that is, it does not excite the production of an antibody which would interfere with the performance of its function. The hormones of the digestive tract are not destroyed by boiling, but are soon oxidised in the body or in the presence of alkalies.

The Gastric Juice Produced by a Normal Meal.—The nervous secretion of gastric juice begins about five minutes after food is taken. By means of this juice digestion in the stomach is initiated and carried on up to a certain point. The semi-digested products of its activity excite the formation of gastrin, by the agency of which the production of the juice is continued as long as the stomach contents require it. The following table from Pawlow illustrates the relative quantity and digestive power of the juice secreted (1) after a normal meal, (2) as a result of the chemical stimulus alone, and (3) after a sham meal, *i.e.* by the nervous secretion alone. The digestive power is measured by filling short lengths of capillary tube with egg-white, coagulating the latter by heat, and placing the tubes, the ends of which are open, in the juice to be tested for a given time. The digestive power is estimated by the length of the column of coagulated protein which has undergone solution.

Hours.	Normal meal. 200 gm. meat into stomach.		150 gm. meat into stomach.		Sham meal.		Sum of two last expts.
	Quantity c.c.	Strength mm. dig.	Quantity c.c.	Strength mm. dig.	Quantity c.c.	Strength mm. dig.	Quantity c.c.
1	12·4	5·43	5·0	2·5	7·7	6·4	12·7
2	13·5	3·63	7·8	2·75	4·5	5·3	12·3
3	7·5	3·5	6·4	3·75	0·6	5·75	7·0
4	4·2	3·12	5·0	3·75	0·0	0·0	5·0

It will be observed that the amount of juice secreted as the result of a normal meal, shown in the first column, corresponds with the totals given in the last column for the nervous and chemical secretions obtained separately.

It has already been pointed out that meat excites the production of gastric secretin and therefore of gastric juice, and that bread, when it has undergone partial digestion, is also an efficient secretogogue. Fat, on the other hand, inhibits gastric secretion, and therefore the flow of juice which results when milk is taken into the stomach is smaller than that which results from a meal of meat or bread. The

flow of juice is also inhibited by alkalies, and is excited by acids in the stomach.

The Origin of the Chief Constituents of the Gastric Juice.—Two chief types of gland are found in the mucous membrane of the stomach. The tubular glands of the body of the stomach are relatively straight, open into short ducts, and possess two kinds of secreting cells. The gland is lined throughout by cubical, granular cells which are called chief or peptic cells. Between the chief cells and the basement membrane there occur at intervals somewhat larger ovoid cells, which are described as oxyntic because they are believed to secrete the acid of the gastric juice. The second type of gland occurs in the pyloric portion of the stomach. The pyloric glands are also simple tubes, which are twisted on themselves and open into relatively long and wide ducts. Moreover, each is lined by one type of cell only, resembling in structure the chief cells of the glands of the body of the stomach.

The cells lining the general surface of the stomach and the ducts secrete the mucin of the gastric juice. The enzymes of the juice are contained in the secretion of the body of the stomach and also in that of the pyloric portion, and are derived from the chief cells of the glands of the body and from the cells lining the pyloric glands. Pepsin, however, does not exist in the secretory cells as such, because extracts of the mucous membrane do not possess marked peptic activity until they have been treated with acid. It is therefore a precursor of pepsin, known as *pepsinogen*, which is found in the secretory cells, and this is converted into pepsin, after its discharge from the cells, by the hydrochloric acid of the gastric juice.

The facts from which it is concluded that the acid itself is derived from the ovoid cells are (1) that it is most abundant in the middle of the stomach, where these cells are most numerous, and (2) that it is absent from the secretion of the pyloric portion of the stomach, where ovoid cells are also wanting.

Various explanations have been offered as to the method of production of the free acid in the gastric juice. The most probable of these suggestions is that the acid is derived from the interaction of chlorides with di-sodium hydrogen phosphate, according to the formula

$$2Na_2HPO_4 + 3CaCl_2 = Ca_3(PO_4)_2 + 4NaCl + 2HCl.$$

During the early stages of secretion the cells of the gastric glands become enlarged, the chief cells, and those lining the pyloric glands, are crowded with secretory granules, and the ovoid cells are distended and clear. As secretion proceeds, all the cells become diminished in size, as in the case of the salivary glands. It has already been pointed out

that pepsin exists in the gland cells in the form of a precursor, and it is probable that lipase, as well as rennin, if the latter exists as an independent ferment, are also represented in the chief and pyloric gland cells as granules of a zymogenic nature.

THE MOVEMENTS OF THE STOMACH.

The movements of the stomach are most conveniently studied by direct observation with the aid of Röntgen rays after the administration of a meal mixed with a quantity of oxychloride of bismuth. In

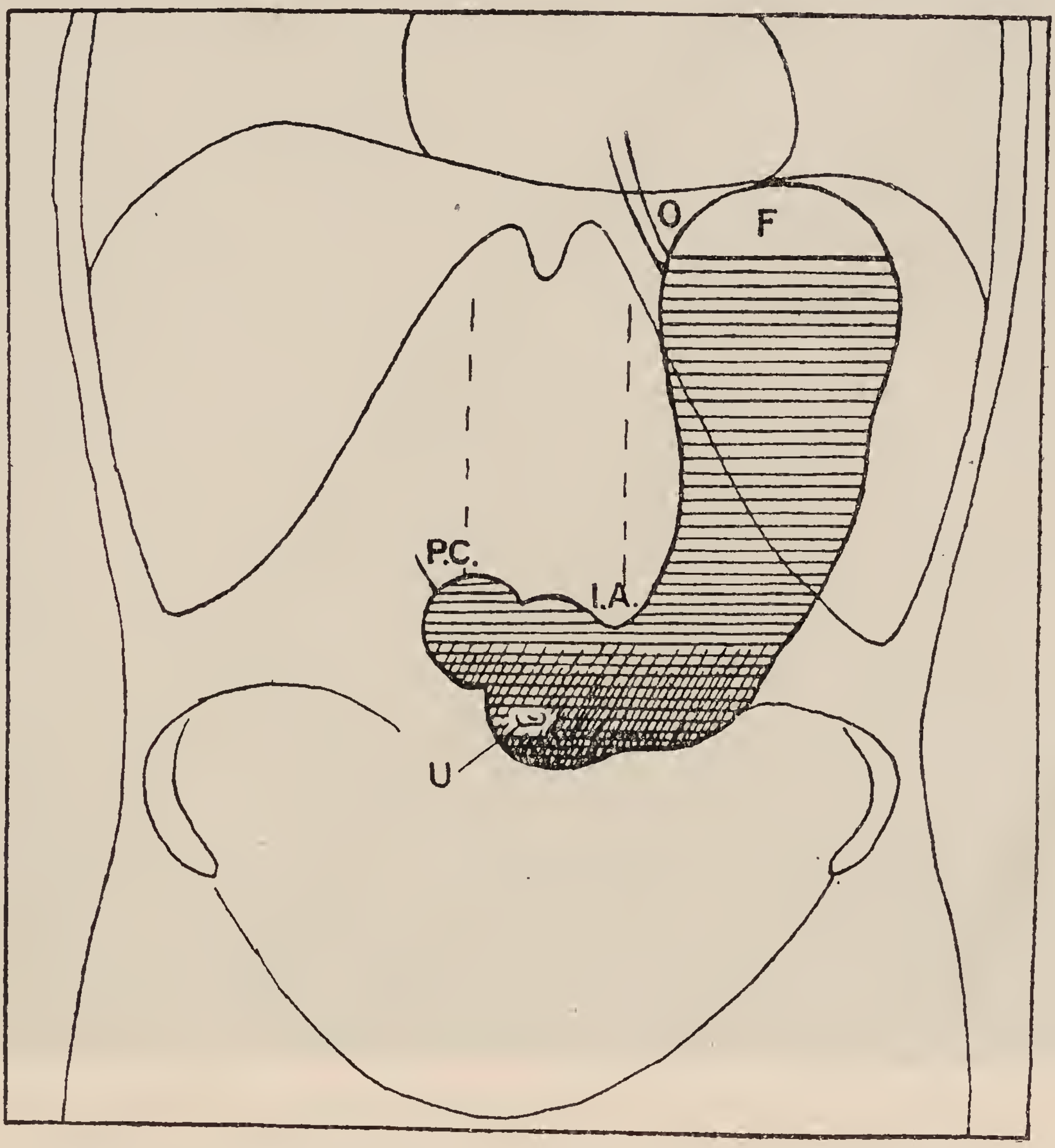


Fig. 120.—Shape of human stomach, in vertical position, shortly after a bismuth meal. (Hertz.)

U, umbilicus; O, œsophagus; F, fundus; P.C., pyloric canal; I.A., incisura angularis.

these circumstances the organ is seen to consist of two parts, the axis of the larger portion being nearly vertical, and forming an angle with the smaller pyloric portion, which is again subdivided by a constriction into two parts, the pyloric vestibule and the pyloric canal (fig. 120). The pyloric canal is about 3 centimetres in length, while the pyloric vestibule or antrum is less constant in size.

After the ingestion of a meal, the muscular walls of the body and

fundus (namely, the dome-shaped part of the organ above the entrance of the œsophagus) become tonically contracted. Waves of contraction occur in the pyloric portion, beginning about the middle of the stomach and travelling at the rate of about three a minute towards the pylorus. The stomach contents are propelled by these waves towards the pylorus, and if the opening is kept closed by the contraction of the

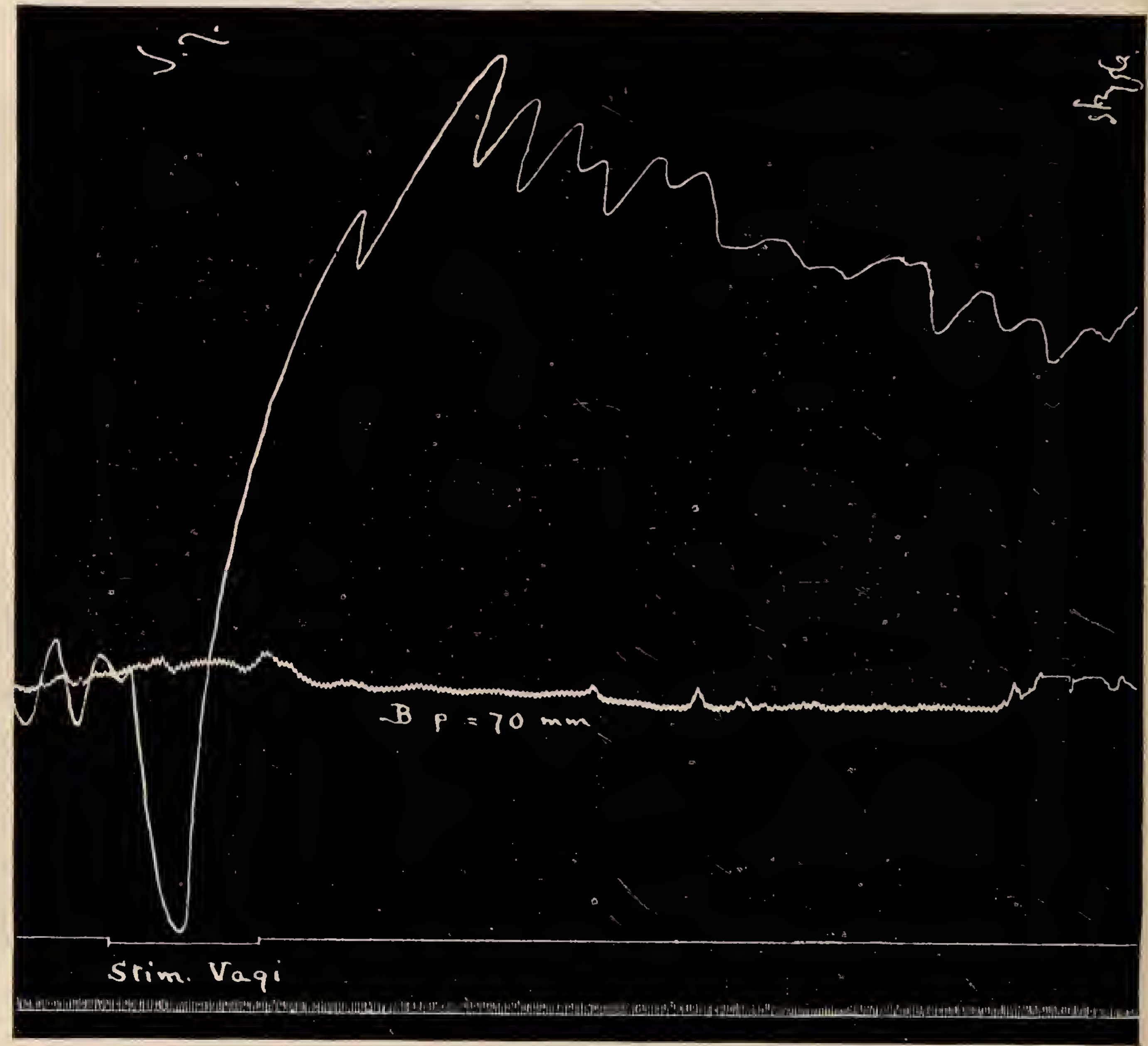


FIG. 121.—Tracing showing initial relaxation followed by contraction of the muscular wall of the stomach on stimulation of vagus nerves. (Elliott.)

sphincter, they return by an axial stream towards the body of the stomach. In this way complete mixture with the gastric juice is effected. As digestion proceeds and the food is brought into a more fluid state, the sphincter undergoes periodic relaxation, opening every few minutes to allow the passage of the semi-liquid material into the duodenum. By the tonic contraction of the fundus and body, the food is little by little subjected to the action of the pyloric mill, and subsequently passed on to the duodenum; and as the contents of the stomach are thus gradually diminished in quantity, the organ becomes

more tubular in shape, until finally, four or five hours after the commencement of digestion, the process is complete.

The precise mechanism by which the movements of the stomach are originated and carried out has not been definitely ascertained. Branches of the vagus nerves and of the sympathetic system are supplied to the viscus, and form connections with the plexus which lies between the layers of the muscular coat. Fine filaments from the latter are distributed to the muscle fibres. Division of the two vagi is followed

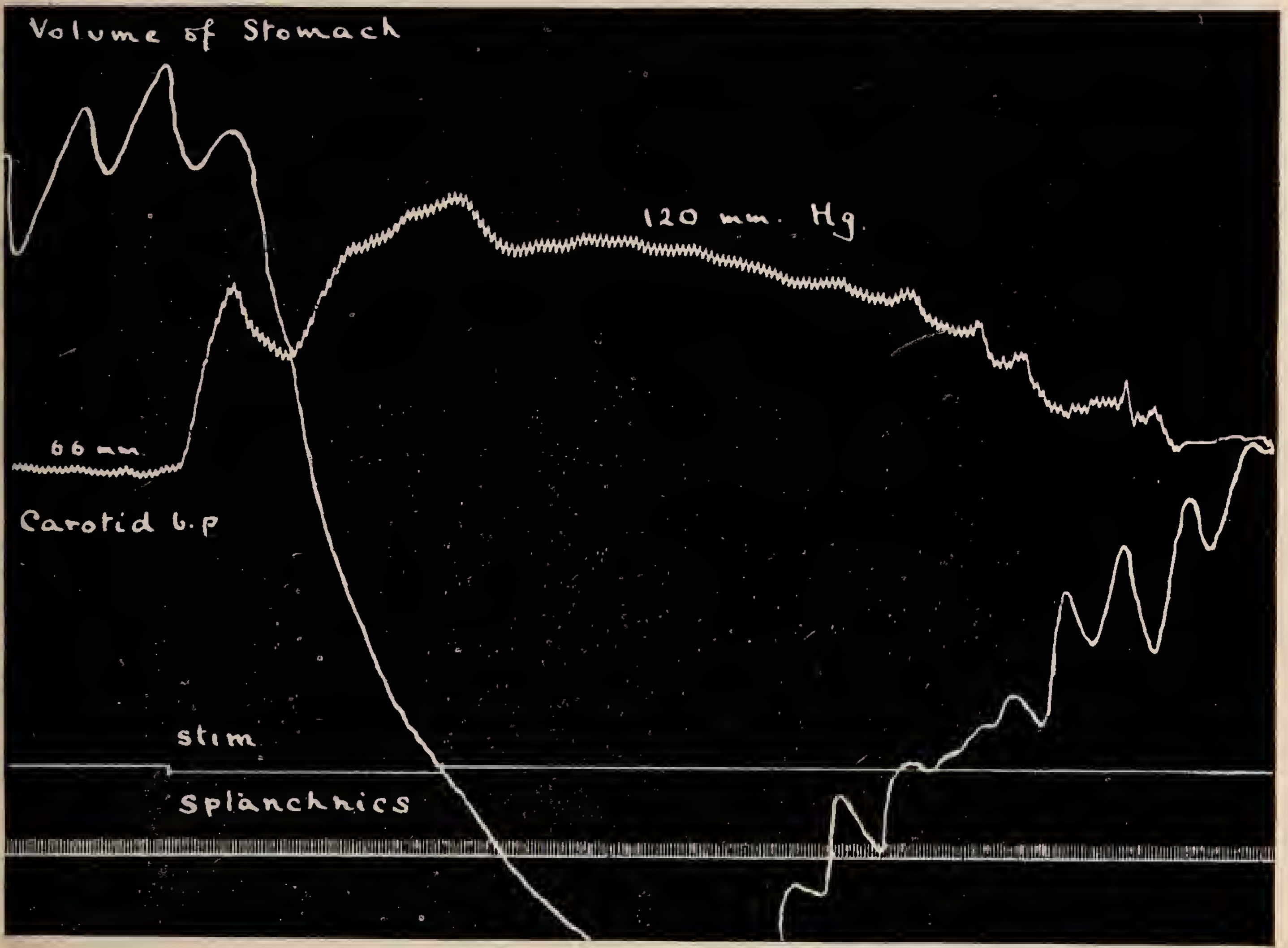


Fig. 122.—Tracing showing relaxation of the muscular wall of the stomach of a cat on stimulation of splanchnic nerves. (Elliott.)

by defective movements, so that the stomach is incompletely emptied after each meal. Stimulation of the vagi leads to temporary diminution of muscular tone, followed by increased contraction (fig. 121), whereas the sympathetic system has on the whole an inhibitory effect on the muscular wall (fig. 122).

The influence of the central nervous system is, however, not essential for the stomach movements, for normal contractions may be observed in the isolated organ placed in warm saline solution. It is still an open question whether these contractions are myogenic in origin, or are due to a local reflex through the plexus in the muscular coat. In any case, the movements may be considered to be under a certain degree of

control by the vagi and the sympathetic, the former having on the whole a motor and the latter an inhibitory effect.

The periodic opening of the pylorus has been experimentally shown to be under the control of a local reflex mechanism, depending on the reaction of the contents in the pyloric portion of the stomach and the duodenum respectively. When the reaction in the duodenum is acid, the pyloric sphincter remains tightly contracted; if, on the other hand, the reaction on the stomach side of the pylorus is acid and on the duodenal side it is neutral or alkaline, the sphincter relaxes. Thus when acid material has passed from stomach to intestine, the pylorus remains closed until the duodenal contents have been neutralised by the alkalies present in the bile and pancreatic juice. When neutralisation has taken place, a further quantity of the gastric contents is allowed to pass through the pyloric opening. The precise nature of the reflex by which this is effected is still uncertain. If a quantity of water is drunk, it does not excite the secretion of gastric juice, the pyloric sphincter is not stimulated to contract, and, if the stomach is empty, the fluid begins to enter the duodenum within one or two minutes of its being taken into the mouth.

SECTION IV.

DIGESTION IN THE SMALL INTESTINE.

If an experimental meal is given to an animal in which a fistula has been made just beyond the pylorus, it is found that food begins to pass from the stomach into the intestine eight to twelve minutes after the meal is taken. The rate of escape of the food from the stomach is indicated in the following table:—

1st hour . . .	32·6	per cent.
2nd ,, . . .	17·9	,, ,,
3rd ,, . . .	29·5	,, ,,
4th ,, . . .	1·87	,, ,,
5th ,, . . .	6·66	,, ,,
6th ,, . . .	4·21	,, ,,

If the material collected in this way is analysed, it is found that 67 per cent. of the nitrogen is in the form of proteose and peptone, and that of the starch of the meal 21 per cent. has been converted into dextrin and 4 per cent. into sugar. The whole of the protein and carbohydrate of the meal is accounted for, no absorption of these substances or of fat having taken place in the stomach. The mixture of semi-

digested substances which enters the intestine has a yellowish colour and a semi-fluid consistence, and is immediately subjected to the action of the pancreatic juice and bile. The secretion of Brunner's glands and the intestinal juice are also mixed with the duodenal contents, but the digestive action of the former is not known to have any importance, and that of the latter has its chief value in the later stages of the digestive process. The action of the pancreatic juice and bile must therefore be considered in the first place.

THE COMPOSITION OF PANCREATIC JUICE.

Pure pancreatic juice may be obtained from an animal either by means of a temporary fistula, made by introducing a cannula into the pancreatic duct, or by a permanent fistula. In the dog there are two ducts, the larger of which opens into the duodenum about an inch below the entry of the bile duct. Pawlow's method of making a permanent fistula is to cut out a patch of the duodenal wall with the opening of the duct in its centre, stitch up the gap in the duodenum, and suture the patch with the opening of the duct into the abdominal wall.

The pancreatic juice obtained in this way is a clear, limpid fluid, having a specific gravity of about 1007 and a strongly alkaline reaction. The degree of alkalinity is such that equal volumes of gastric juice and pancreatic juice neutralise each other. The concentration of pancreatic juice varies considerably, but it contains on an average about 4 per cent. of solids. These consist of nucleo-protein, enzymes or their precursors, and inorganic salts. The chief salt is sodium carbonate.

THE FUNCTIONS OF PANCREATIC JUICE.

The action of the pancreatic juice on the constituents of the food may be studied in test tubes, using either the secretion obtained from a fistula, or an artificial juice made by adding a glycerol extract of the fresh gland to a solution of sodium carbonate of such a strength that the mixture contains 0·5 per cent. of the carbonate.

The Action of Pancreatic Juice on Proteins.—Pure pancreatic juice, obtained directly from the pancreatic duct, without contact with the intestinal mucous membrane, has no action on proteins. If, however, the juice has flowed over the duodenal mucous membrane or has been mixed with intestinal juice, it is strongly proteolytic. The pure juice contains a substance, *trypsinogen*, which is the precursor of a proteolytic

enzyme, *trypsin*, and is converted into the latter by another ferment, *enterokinase*, produced in the mucous membrane of the small intestine. Trypsinogen may also be converted into trypsin by other means, for example by the action of lime salts; or the activation will slowly take place spontaneously if the juice is allowed to stand. Activation is, however, effected most rapidly by enterokinase, requiring a few minutes in the case of this ferment as against over twelve hours by means of calcium.

If a few flakes of fibrin are placed in a solution containing trypsin and 0·5 per cent. sodium carbonate in a test tube, and kept at a temperature of 37° C., the fibrin will begin to be eroded in a few minutes, and gradually it will become dissolved. The products in solution will vary according to the time during which digestion has been allowed to proceed, but generally speaking the course of hydrolysis is the same as in peptic digestion, except that, as the process takes place in an alkaline medium, the metaprotein formed is the alkaline and not the acid variety. A second point of difference is that the intermediate stages are passed through more rapidly in pancreatic than in gastric digestion, and thirdly, some amino-acid is produced even in the time available for digestion in the intestine.

In the normal course of digestion in the intestine, the final conversion of peptone into amino-acids is largely effected by the ferment *erepsin*, which is contained in the intestinal juice; but almost complete hydrolysis into amino-acids can be obtained *in vitro* by means of trypsin, if the digestion is allowed to proceed for three or four days. The splitting is not quite complete, for even if the digestion has been allowed to go on for some weeks some amino-acids remain united in groups of two or more, known as *polypeptides*. These latter substances have much smaller molecules than peptones and do not give the biuret reaction, that is, they do not give a pink colour with copper sulphate and caustic soda.

If a tryptic digestion of fibrin or casein has been allowed to proceed for some days, the solution contains the amino-acids derived from these substances (p. 13). Leucine and tyrosine are most easily demonstrated in the fluid, and crystallise out readily if the fluid is concentrated. Tyrosine appears as sheaves of colourless needles, and leucine, which is the more soluble of the two, occurs in the form of yellowish balls, which sometimes show concentric and radial striation. Solutions of tyrosine, when boiled with Millon's reagent, give a red colour.

The stages of tryptic digestion may be represented in tabular form thus:—

Protein
↓
Soluble globulin
↓
Alkali metaprotein
↓
Primary proteoses
↓
Secondary proteoses
↓
Peptones
↓
Polypeptides and Amino-acids.

The earlier stages of tryptic digestion of protein are most efficiently carried out in a slightly alkaline medium, but the ferment is active in either an alkaline or neutral solution. Under natural conditions, the alkalinity of the pancreatic juice is largely neutralised by the acid contents from the stomach, and the contents of the small intestine throughout its length are almost neutral. The activity of trypsin diminishes during the course of normal digestion, since the ferment enters into combination with the products of its own activity, that is, with amino-acids and peptones, and in this way it becomes inactive. The intestinal contents taken from the lower end of the ileum show little trace of tryptic activity.

The Action of Pancreatic Juice on Starch.—The action of pancreatic juice upon starch depends on the presence of an enzyme, *amylase*. By means of this ferment starch is converted into maltose, as in the case of salivary digestion (p. 293), but the action of pancreatic amylase is more rapid and powerful than that of the ptyalin of saliva. If some pancreatic extract is added to dilute starch paste kept at a temperature of 37° C., the soluble starch stage is reached in a few seconds and erythro-dextrin may be detected in half a minute. Moreover, the pancreatic juice is capable of digesting unboiled starch, on which saliva has no action.

As maltose is formed it is further hydrolysed, partly by a ferment *maltase*, contained in the pancreatic juice, and partly by a similar ferment found in the intestinal juice. Under the influence of maltase each molecule of maltose takes up a molecule of water and is split into two molecules of dextrose.

$$C_{12}H_{22}O_{11} + H_2O = 2C_6H_{12}O_6.$$

Pancreatic juice differs, however, from intestinal juice in having no similar action on the other disaccharides, lactose and cane sugar.

The Action of Pancreatic Juice on Fats.—If perfectly neutral fat,

such as pure olive oil, be shaken up with pancreatic juice, and the mixture be kept at a temperature of 37° C., the fatty ester will be hydrolysed, yielding fatty acid and glycerol, and the reaction of the fluid will become acid. The agent which brings about this change is an enzyme, *lipase*, which is a constituent of the pancreatic juice. Lipase may be extracted from the fresh pancreas by glycerol, but not by water. The fat-splitting action of lipase is greatly facilitated by the presence of bile, taking place four or five times as rapidly when assisted by bile as in its absence. This acceleration is due to the bile salts, which not only reduce surface tension and so promote the admixture of the enzyme and the fats, but also have the property of bringing fatty acids and soaps into solution.

The digestion of the fats is further assisted mechanically by the formation of soaps. Some of the fatty acid which is set free combines with the alkalies of the intestinal contents to form soap. Segmental contractions of the intestine lead to the mechanical subdivision of the fats with the formation of an emulsion. Each fat droplet becomes coated with a fine film of soap, which prevents it from coalescing with others, and in this way the formation of a still finer emulsion is favoured, and the fat is made more accessible to the enzyme.

The Action of Pancreatic Juice on Milk.—A milk-curdling ferment has been described as occurring in the pancreatic juice, and it is a fact that clotting of milk takes place when the juice is mixed with milk at the body temperature. It is doubtful, however, whether a separate rennet ferment is present in the pancreatic secretion, and the milk-curdling function has been ascribed by some authorities to trypsin. In any case the clot stage is very brief, for the curd is rapidly dissolved by the proteolytic action of trypsin; moreover, the presence of rennin in the pancreatic juice would seem to be unnecessary in view of the active milk-curdling property of gastric juice.

THE SECRETION OF PANCREATIC JUICE.

In an animal with a permanent pancreatic fistula, a flow of juice is seen to begin within five to twenty minutes after the ingestion of a meal. The secretion is largely increased two or three hours later, when the stomach contents are passing into the duodenum in largest amount, and it comes to an end in about five hours. The following record of two of Pawlow's experiments shows the rate of flow :—

PANCREATIC SECRETION AFTER A MEAL OF 600 C.C. OF MILK.

Hour after Feeding.	Quantity of Juice in c.c.	
1st . . .	8·75	8·25
2nd . . .	7·5	6·0
3rd . . .	22·5	23·3
4th . . .	9·0	6·25
5th . . .	2·0	1·5
Total . .	49·75	45·3

Bayliss and Starling have shown that the secretion of pancreatic juice is almost entirely due to a hormone, which they have called *secretin*, and which is formed in the mucous membrane of the small intestine. The production of the hormone is brought about by the presence of acid in the intestine, and the normal stimulus for its formation is the passage of the acid gastric contents into the duodenum.

Much work has been done with a view to determining whether a nervous factor is concerned in the production of pancreatic juice, comparable with the reflex which brings about the first secretion of gastric juice; and Pawlow has shown that stimulation of the vagus will excite a small flow of pancreatic juice, even when the pylorus of the stomach is ligatured so as to prevent the passage of the acid contents of the stomach into the duodenum. The amount secreted as the result of vagus stimulation is, however, so small that the nervous factor is obviously of subsidiary importance in the case of the pancreas. It is possible that the first few c.c. of juice secreted may be nervous in origin, because the juice first formed appears a few minutes after a meal is taken, and further, it differs in character from the later formed juice, being more viscid, richer in ferments and in protein constituents and poorer in alkali than the latter.

The later flow is, however, the essential secretion, and that it is due to the formation of a hormone is proved by experiment. If 0·4 per cent. hydrochloric acid is introduced into the duodenum, a flow of pancreatic juice is evoked within two or three minutes. The secretion induced in this way occurs even if the nerves to the intestine have been divided, so that it must be due to the production of some chemical substance which is conveyed to the pancreas. This substance is secretin, and it may be extracted from the duodenal mucous membrane by grinding it with sand and boiling with 0·4 per cent. hydrochloric acid. If alkali be added to

the boiled fluid till it is almost neutral, the proteins are precipitated, and a protein-free filtrate may be obtained. Injection of the filtrate into a blood-vessel of another animal excites the production of pancreatic juice. From this experiment it is obvious that the hormone is not destroyed by acid or by boiling; it is, however, readily destroyed by alkalies. Secretin is absorbed by the blood directly, and does not normally reach the lumen of the intestine; and its introduction into the duodenum does not lead to a flow of pancreatic juice.

The epithelial cells of the intestinal wall form in the first instance a precursor of secretin, called *prosecretin*. Secretin itself is freely soluble in water and alcohol, but an extract of intestinal mucous membrane made with either of these fluids contains neither secretin nor prosecretin. The latter substance, therefore, is insoluble in water and alcohol, and is converted into secretin on boiling with dilute hydrochloric acid.

Prosecretin is most abundant in the duodenum, it occurs also to a considerable extent in the jejunum, and to a less degree in the ileum; but near the junction of the small and large intestines it is formed in very small amount.

The amount of secretin formed in the body, as shown by the volume of pancreatic juice secreted, varies with the nature of the food. After a meal of bread or meat the flow of juice is more abundant, and reaches its maximum more rapidly, than after a meal of milk. The reason of this difference is that meat or semi-digested bread stimulates the production of gastric secretin and thus causes a large flow of gastric juice, whereas milk is a less efficient stimulus to gastric secretion. As a result, more acid reaches the duodenum after a meal of bread or meat than after the ingestion of milk, and therefore more secretin is produced in the former case than in the latter. On the other hand, the fatty acids formed by the action of gastric lipase on milk are converted into soaps in the duodenum. Soaps stimulate the production of secretin, and the delayed maximal production of pancreatic juice after a meal of milk may be explained by a second formation of secretin in this way.

The Changes in the Pancreas which accompany Secretion.—The pancreas is a compound tubular gland, and it contains, in addition to the ordinary secretory tubules, clumps of cells which do not stain deeply with the ordinary dyes, and which are known as cell-islets (fig. 130). These islets are supposed to be concerned with the formation of an internal secretion, and their function will be discussed in connection with metabolism. The secretory tubules of the pancreas are lined by a single layer of columnar cells, each of which shows two zones—an outer, which stains with basic dyes such as hæmatoxylin or

toluidin blue, and an inner, filled, in the resting stage of the gland, with secretory granules. The granules stain well with osmic acid, eosin, or neutral gentian.

After a prolonged period of secretory activity the granules are greatly diminished in number, and the inner zone of the cell is relatively and absolutely smaller as compared with the outer zone. Under normal conditions this diminution of the inner zone does not occur, because the formation of new granules keeps pace with the extrusion of those previously formed, so that the appearance of the cells is little altered by the secretion required for an ordinary meal. The secretory granules are in all probability zymogenic, and represent the precursors of the enzymes found in the juice. In the case of trypsinogen, the precursor has received the name of protrypsinogen.

THE BILE.

The bile is not a digestive juice in the same sense in which saliva and the gastric and pancreatic juices belong to that category. It is to be looked upon as an excretion, which incidentally assists the digestive action of the pancreatic juice. The production of bile is constant, although the rate of formation varies with the period of the day and other circumstances, and, as it is formed, the secretion is stored in the gall-bladder. This reservoir discharges the accumulated bile into the intestine simultaneously with the great flow of pancreatic juice, which takes place during the third hour of digestion of a meal. The mechanism by which this emptying of the gall-bladder is effected has not yet been definitely ascertained.

THE COMPOSITION OF THE BILE.

Bile may be obtained for analysis from the gall-bladder of a recently killed animal, or it may be collected from a gall-bladder fistula during life. Its composition, however, is not the same in the two cases, fistula bile being more dilute than bile which has been stored for a time in the gall-bladder. The difference is shown in the following two analyses of human bile by different observers :—

Fistula Bile.		Gall-bladder Bile.	
Mucin and pigments	0·148	Mucin	1·29
Sodium taurocholate	0·055	Sodium taurocholate	0·87
Sodium glycocholate	0·165	Sodium glycocholate	3·03
Cholesterol	...	Cholesterol	0·35
Lecithin	0·038	Lecithin	0·53
Fats	...	Fats	0·73
Inorganic salts	0·840	Soaps	1·39
Water	98·7		

Bile thus becomes more concentrated by the absorption of water during the time it remains in the gall-bladder. It is a viscid fluid, golden brown in carnivora, green in herbivora, and possesses a bitter taste. The viscidity is due to the presence of mucin in human bile, and of a nucleo-protein in that of the ox and some other animals. The colour depends upon the presence of the bile pigments, bilirubin and biliverdin. The former is more abundant in the bile of carnivora, the latter in the bile of herbivora. The proportion appears to vary in human bile according to the nature of the diet, the brown tint of bilirubin predominating when a flesh diet is taken, and the green of biliverdin when the diet is largely vegetarian. The bitter taste of bile is due to the bile salts, glycocholate and taurocholate of sodium. In dog's bile the latter only is present.

The Properties, Source, and Fate of the Chief Constituents of the Bile.—The *mucin* of human bile gives a stringy precipitate on the addition of acetic acid, the precipitate being insoluble in excess of the acid. The nucleo-protein of ox bile gives a similar precipitate with acetic acid, but as in the case of nucleo-proteins generally, the precipitate is dissolved by excess of the acid. The mucin or nucleo-protein of the bile is derived from the mucus-secreting cells which line the bile ducts and gall-bladder.

The *bile salts* are compounds of sodium with glycocholic and taurocholic acid respectively. These acids may be split up by hydrolysis, glycocholic into glycine (amino-acetic acid) and cholic acid, and taurocholic into taurine (amino-ethylsulphonic acid) and cholic acid.

$$\underset{\text{Glycocholic acid.}}{C_{26}H_{43}NO_6} + H_2O = \underset{\text{Glycine.}}{CH_2 . NH_2 . COOH} + \underset{\text{Cholic acid.}}{C_{24}H_{40}O_5}$$

$$\underset{\text{Taurocholic acid.}}{C_{26}H_{45}NO_7S} + H_2O = \underset{\text{Taurine.}}{C_2H_4 . NH_2 . HSO_3} + \underset{\text{Cholic acid.}}{C_{24}H_{40}O_5}$$

If a little syrup of cane sugar be added to a solution of bile salts in a test tube, and strong sulphuric acid be poured down the side of the tube so as to lie below the solution, a cherry-red colour appears at the junction of the two fluids. The colour is due to a reaction between cholic acid and furfuraldehyde, the latter being formed by the action of the sulphuric acid on the cane sugar. The bile salts have the property of reducing the surface tension of the fluid in which they are dissolved. This can be shown by comparing the effect of scattering flowers of sulphur on water and on a solution of bile salts. The sulphur floats on the water, but sinks immediately in the bile salt solution (Hay's test). Further, watery solutions of bile salts readily dissolve fatty acids. Bile acids are derived from protein sources and are formed

in the liver. The larger proportion of the bile salts which pass into the intestine is reabsorbed and returns to the liver to enter again into the composition of bile. This is spoken of as the circulation of the bile salts, and not only do these substances enter once more into the formation of bile, but they also stimulate the liver to further secretion, that is, they act as cholagogues. A small proportion of the bile salts is excreted in the fæces in the form of dyslysin, a substance formed from them by bacterial decomposition. Part of the sulphur excretion from the body takes place in this way, since this element forms part of the taurine molecule.

Cholesterol (p. 8) and *lecithin* (p. 8) are probably largely derived from the stroma of the red blood corpuscles which are broken down in the liver. Gall-stones, which are of fairly common occurrence in the gall-bladder, are usually composed chiefly of cholesterol. Normally the latter substance is excreted in the fæces.

The *bile pigments* are characterised by their colour and by the fact that they are easily oxidised by nitrous acid, yielding a series of coloured products (Gmelin's test). If nitric acid containing nitrous acid is added to bile in which the pigment present is bilirubin, the colour changes to green (biliverdin), then to blue, violet, red, and finally to yellow (choletelin). Bilirubin and biliverdin show no absorption bands with the spectroscope. Bilirubin ($C_{16}H_{18}N_2O_3$) is identical with hæmatoidin, a substance formed by the decomposition of hæmoglobin in old blood clots in the body. Its molecule only differs from that of iron-free hæmatin, formed by the action of strong mineral acids on hæmoglobin, in possessing one atom less of oxygen.

Bile pigments are derived from the pigment of the blood by the breaking down of the latter in the liver. The facts upon which this statement is based are (1) the identity of bilirubin with hæmatoidin, (2) histological observations on the liver, (3) observations on the proportion which exists between the rate of destruction of the red blood corpuscles and the amount of bile pigment formed, and (4) the effect of injection of hæmoglobin into the blood stream. Histological observations show that the walls of the sinusoids in the liver are incomplete, so that red blood corpuscles can pass through them; and red corpuscles, broken up to a greater or less degree, have been seen within the liver cells. Moreover, the presence of iron in the liver cells can be demonstrated by the blue colour produced by treatment of sections with ferrocyanide of potassium and hydrochloric acid. Again, when the destruction of red blood corpuscles is increased, as in the disease known as pernicious anæmia, or in poisoning by the injection of pyrogallic acid or toluylene diamine, the amount of bile

pigment produced is excessive and the iron in the liver cells is increased. Finally, when a solution of hæmoglobin is injected into the blood stream, there is an increased production of bile pigment.

The bile pigments undergo bacterial decomposition in the large intestine with the formation of *stercobilin*, the pigment of the fæces. Some of the latter is reabsorbed, and appears in the urine as a chromogenic substance, urobilinogen, from which urobilin is formed by oxidation. Urobilin itself is identical with stercobilin, and it occurs in the urine in pernicious anæmia and other diseases in which destruction of red blood corpuscles is excessive.

THE FUNCTIONS OF THE BILE.

It has already been pointed out that bile is not a digestive juice in the proper sense of the term. It is said to contain a weak amylolytic enzyme, but the action of this ferment is quite insignificant. Nevertheless the bile exercises important functions in connection with the digestive process. (1) The acid metaprotein and proteoses resulting from the gastric digestion of proteins are precipitated by the bile salts in the duodenum. This conversion of a fluid or semi-fluid material into the solid condition will retard its progress along the intestine and allow more time for the action of the pancreatic juice. (2) The bile salts act as a "co-enzyme" to each of the principal ferments of the pancreatic juice, that is, they increase the rate of the digestive process without themselves taking any active part in it. In the presence of bile salts the power of the pancreatic amylase to hydrolyse starch is doubled, and the proteolytic power of trypsin is similarly increased, while the action of lipase upon fats is quadrupled. The adjuvant action of bile in digestion is due to the property which the bile salts possess of reducing surface tension, as well as to their property of dissolving fatty acids and soaps. By the reduction of surface tension the contact of enzyme with substrate is promoted, and this is of especial value in facilitating the access of lipase to oily fluids. (3) Bile promotes the absorption of the products of digestion, this property also being due to the bile salts. Free fatty acids are brought into solution, and in this form are more adapted for passing through the epithelial cells of the intestinal villi. Moreover, these cells have their surface tension lowered, and are thus made more permeable by all the products of digestion. Lecithin and cholesterol, which are held in solution in the bile, also play a part in promoting absorption, but the precise way in which they act is not understood. The importance of the presence of bile for the digestion and absorption of fat is shown by the fact that when bile is prevented from entering

the intestine, 60 per cent. of the fat of a meal passes into the fæces, as compared with about 5 per cent. under normal conditions. (4) Bile is said to stimulate the peristaltic movements of the intestine, and (5), as already pointed out, the reabsorbed bile salts stimulate the liver to further secretion.

THE SECRETION OF BILE.

The secretion of bile is a continuous process, and in periods when digestion is not taking place, bile accumulates in the gall-bladder. About the third hour after a meal is taken the gall-bladder is emptied into the lumen of the duodenum, but the mechanism by which the contents are expelled has not yet been ascertained. Bile continues to flow into the intestine during the digestive process, and, later, again accumulates in the gall-bladder. The rate of production of bile has been studied in animals with experimental fistulæ, and also in man when fistulæ have formed in the course of disease. In such cases, however, the normal stimulus due to the reabsorption of bile salts is wanting. It is found in man that something less than a litre of bile can be collected from a fistula in twenty-four hours, an amount equal to that of the juice secreted by the pancreas in the same time.

So far as is known, the secretion of bile is independent of nervous action, and is excited (1) by the reabsorbed bile salts, and (2) by secretin. The flow from a fistula is fairly continuous, though it varies in rate with the period of the day and with other conditions. The rate of flow in such a case is, of course, unaffected by reabsorption of bile salts. It is doubled by the introduction of dilute hydrochloric acid into the duodenum, or by the injection of secretin into the blood stream. The rate of flow, like that of the pancreatic juice, varies with the nature of the food, and for the same reason (p. 318), being greatest when a meat diet is taken, and least when the food consists mainly of carbohydrates. Fatty food, which inhibits the secretion of gastric juice, excites the secretion of the pancreas and liver, though not to the same extent as does meat. The influence of fat in this direction is due to the formation of soap in the duodenum, the latter substance acting as a stimulus to the production of secretin.

THE FINAL STAGES OF THE DIGESTIVE PROCESS.

Saliva, gastric and pancreatic juice in turn carry the digestion of the food-stuffs up to a certain point. The pancreatic juice completes the digestion of the fats; it converts proteins into peptones and amino-acids; it is capable of converting starch completely into dextrose, but it has no action upon cane sugar and lactose. The completion of the digestive process is the function of the intestinal juice.

THE COMPOSITION OF THE INTESTINAL JUICE.

Intestinal juice is obtained, like the other digestive secretions, by means of a fistula. A segment of intestine of sufficient length is separated by incisions; one end of the separated portion is closed by sutures, and the open extremity is sutured into the abdominal wall, the continuity of the remainder of the bowel being restored by stitching the free ends together. The detached segment retains its normal blood and nerve supply. In another method, both ends of the segment are left open, and each is sutured separately into the abdominal wall (fig. 123).

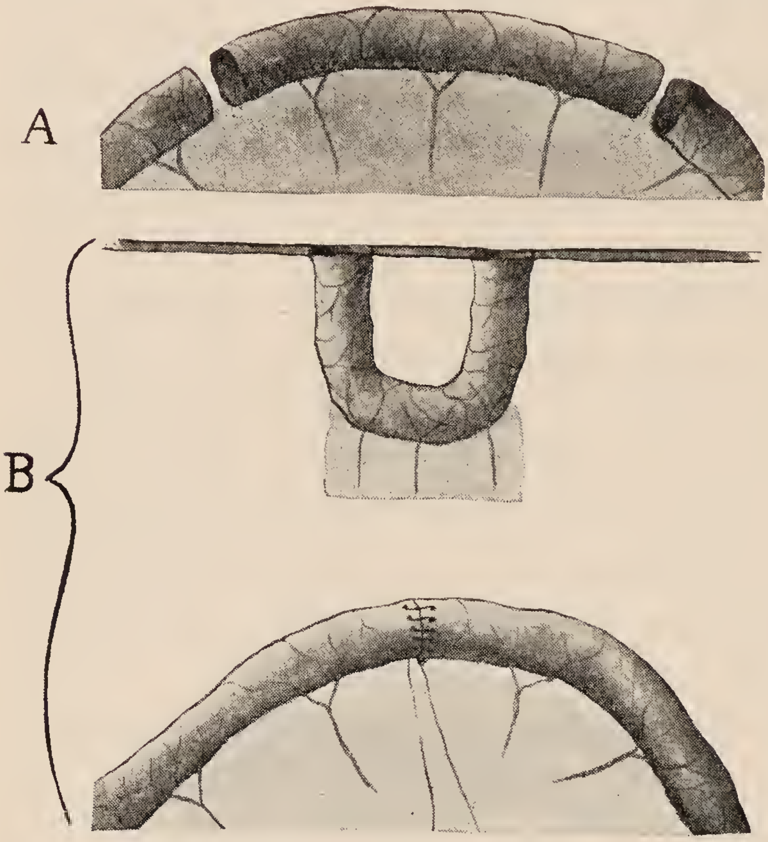


Fig. 123.—Scheme of intestinal fistula. A, first stage of operation; B, fistula completed.

The juice obtained from such a fistula has a specific gravity of about 1010, and is alkaline. It contains 1 to 2 per cent. of solids, half of which are organic and half inorganic. The organic solids consist mainly of serum albumin, serum globulin, and enzymes. The inorganic substances are chiefly sodium chloride and sodium carbonate.

THE FUNCTIONS OF THE INTESTINAL JUICE.

It has already been pointed out that the intestinal juice converts trypsinogen into trypsin by virtue of the enzyme, *enterokinasé*, which it contains, and also that another of its enzymes, *maltase*, shares with a similar ferment in the pancreatic juice the function of completing the digestion of starch by converting maltose into dextrose. The intestinal juice also contains two enzymes which convert the disaccharides, cane sugar and lactose, into monosaccharides. One of these ferments, *invertase*, converts a molecule of cane sugar into one molecule of dextrose and one molecule of fructose. The other, *lactase*, hydrolyses lactose in a similar way into dextrose and galactose. Lactase is most abundant in young animals, at the period of life when lactose is an important constituent of the dietary. The terminal stages of the hydrolysis of protein are effected by a ferment, *erepsin*, existing in

the intestinal juice. Erepsin acts upon proteoses and peptones, splitting them up into amino-acids. There is some ground for believing that the hydrolysis is not quite complete, and that, in the final result, in addition to amino-acids, there are some more complex substances called polypeptides, groupings of amino-acids which are less complex than peptones, and which do not undergo complete hydrolysis. Erepsin is also contained in the epithelial cells covering the villi, and it is possible that the final stages of hydrolysis may occur in these cells.

The chief amino-acids resulting from the digestion of proteins are leucine, tyrosine, aspartic acid, glutaminic acid, tryptophane, and the hexone bases, lysine, arginine, and histidine. These, and other substances belonging to the same group, are linked together to form the protein molecule, and the differences found to exist between the various proteins are associated with differences in the proportions of their constituent amino-acids.

The intestinal juice is produced by the crypts of Lieberkühn, tubular glands lined by columnar epithelium, occurring in the mucous membrane of the small intestine, and opening between the bases of the villi. There is no evidence that the secretion is influenced by a nervous factor. If three adjacent loops of intestine are separated from each other by ligatures, and the nerves to the middle loop are divided, the latter is found full of fluid after four to sixteen hours, while the adjacent loops are empty. Two days later, however, all three loops are empty. It appears probable, therefore, that the production of fluid following the section of the nerves is due to dilatation of blood-vessels resulting from the division of vaso-constrictor nerves, and that absorption occurs and the production of fluid ceases as the vessels regain their tone. No conclusions can therefore be drawn as to an inhibitory or other influence of the nervous system on the secretion from such an experiment. The normal stimulus for the secretion of the intestinal juice is undoubtedly secretin, and possibly also other hormones. This possibility is supported by the fact that intestinal juice is produced in the dog about ten minutes after the ingestion of a meal of meat, and that the flow is increased in the third hour after the food has been taken. The secretion of intestinal juice can be brought about by mechanical stimulation, probably by means of a local nervous mechanism.

THE PROGRESS OF DIGESTION IN THE SMALL INTESTINE.

Experiments have been made on dogs in which the intestinal contents were withdrawn, by means of appropriate fistulæ, at different stages of their passage along the bowel. It was found that after a

test meal 77 per cent. of the protein was converted into proteose and peptone, and one-half to three-fifths of the starch into dextrin and sugar, as a result of gastric and duodenal digestion, and that, when the intestinal contents reached the lower end of the ileum, the digestion of all the food-stuffs was complete.

THE MOVEMENTS OF THE SMALL INTESTINE.

The intestinal contents are slowly propelled along the gut towards the colon, and at the same time they are subjected to a continuous mixing process. The onward movement is effected by waves of contraction which sweep along the muscular coat of the bowel, and constitute what is known as *peristalsis.* The mixing of the material in the intestine is brought about by ring-like or *segmental contractions*, which are not progressive in character. These movements may be observed in the living animal or person by the aid of Röntgen rays after the administration of a bismuth meal. They can also be observed directly, if the abdomen is opened in an animal immediately after it has been killed. The movements may be recorded in the living animal by means of a balloon inserted into the lumen of the bowel and connected with a writing tambour; contraction of the intestinal wall compresses the balloon, and air is forced into the tambour, thereby raising the lever. Other experimental methods may also be used.

The Peristaltic Movements.—Any mechanical stimulus, such as pinching the intestine, will set up a peristaltic wave. The normal stimulus is a bolus in the lumen of the gut, and it is for this reason that the indigestible material of vegetable food is of value in promoting peristalsis. There are two features characteristic of the peristaltic wave. First, it is preceded by a wave of relaxation which begins below the point of stimulation, the contraction wave itself beginning above that point. Second, it always travels in the aboral direction. If a segment of the intestine be excised and again stitched in position in a reversed direction, the peristaltic waves in the reversed segment will be opposed to those of the rest of the intestine, and partial obstruction to the passage of the intestinal contents will result. Peristalsis still occurs when all connections with the central nervous system have been divided, but it is abolished by painting the gut with nicotine or cocaine. We may conclude, therefore, that it is effected by a local reflex mechanism connected with Auerbach's plexus (the myenteric plexus) in the muscular coat, the stimulus arising from the presence of a bolus in the intestine, and depending upon either the stretching of the intestinal wall or the irritation of nerve endings in the mucous

membrane. This is the only known local reflex, with the possible exception of the opening and closing of the pyloric sphincter.

The Segmental Contractions.—The segmental contractions differ from the peristaltic waves in occurring regularly and rhythmically. When they are recorded by means of a balloon in the intestinal lumen, they are found to be most marked at the middle of the balloon where the tension is greatest. The result of such contractions is to subdivide any bolus over which the contraction takes place, and thus to bring about a thorough admixture of the intestinal contents. Both layers of the muscular coat take part in these contractions, as well as

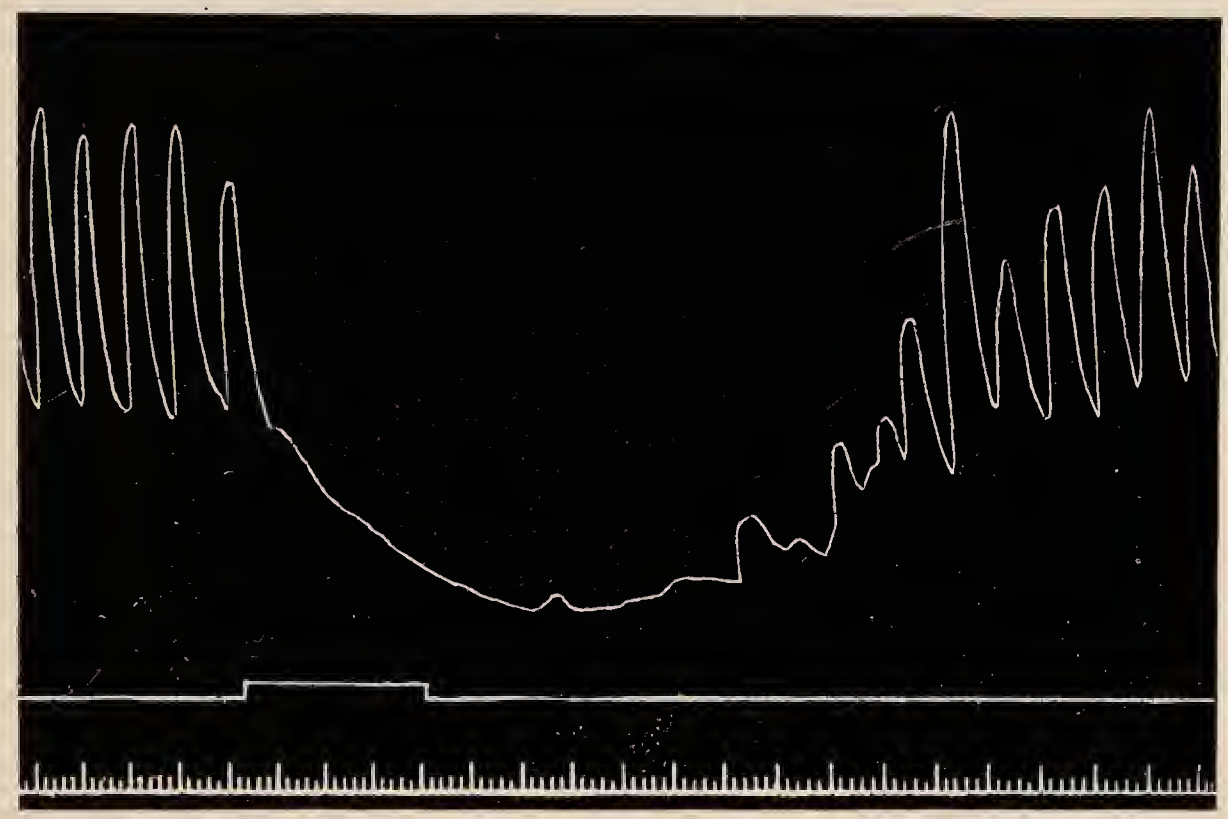


FIG. 124.—Tracing showing relaxation of intestinal wall on stimulation of splanchnic nerve (balloon method). (Bayliss and Starling.)

in the peristaltic waves, and as a result the bowel exhibits pendular or swaying movements. The segmental contractions have no influence in promoting the onward movement of the intestinal contents.

It has not been definitely determined whether the segmental movements are myogenic or neurogenic in origin, though the latter seems the more probable. They are not abolished by painting the intestine with nicotine or cocaine, and this would point to their being of myogenic origin; on the other hand, they occur in isolated strips of muscular coat to which the myenteric plexus is attached, and do not occur if the plexus is absent, so that the presence of the plexus would seem to be necessary for them to take place.

The Nerves of the Small Intestine.—The small intestine is supplied by the vagus and the splanchnic nerves, and although, as has been

pointed out, the intestinal movements are independent of the central nervous system, it can be shown that these nerves exert a controlling influence. Stimulation of the vagus is followed by contraction of the muscle of the intestinal wall after a preliminary relaxation, but has no effect on the ileo-colic sphincter. Stimulation of the splanchnic nerve results in a general relaxation (fig. 124), but in contraction of the ileo-colic sphincter. The vagus and sympathetic fibres to the small intestine are distributed in the first instance to the myenteric nerve plexus lying between the layers of the muscular coat. The influence of the central nervous system on the intestinal movements is shown in their inhibition as a result of pain, and also in their exaggeration in consequence of emotional conditions. The movements of the intestinal wall are increased by pilocarpine, which stimulates the nerve endings of the vagus. The nerve endings are paralysed by atropine, the effect of which is antagonistic to that of pilocarpine.

The Passage of the Intestinal Contents from the Ileum into the Cæcum.—Observations with the aid of Röntgen rays show that the material in the small bowel tends to accumulate behind the ileo-colic sphincter, and that it passes into the cæcum in considerable quantity when the sphincter relaxes. The immediate cause of the relaxation of the sphincter appears to be a nervous reflex (gastro-ileac), which follows the entrance of a fresh meal into the stomach. The delay in the ileum will obviously favour the absorption of the last traces of nutritive substances.

SECTION V.

ABSORPTION IN THE SMALL INTESTINE.

The absorption of the food-stuffs is almost entirely limited to the small intestine. It has been proved that no water is absorbed in the stomach, and although some experiments have seemed to indicate that there may possibly be some absorption of peptone, sugar, and more especially alcohol in that organ, the quantities concerned are, at the most, so small as to be negligible. It will be shown later that a large amount of water is absorbed in the large intestine, and that there is a possibility of the absorption of small amounts of dextrose there also, but, under normal circumstances, the material which reaches the large bowel is free from sugar, as well as all other nutritive digestive products.

The progress of absorption can be investigated by the method already referred to of collecting the intestinal contents by means of fistulæ after the ingestion of a weighed meal. For example, after a

meal of 200 grams of bread given to a dog, the following results were obtained :—

Fistula.	Obtained.	Absorbed per cent.
Pyloric . . .	691 grams.	0
Duodenal . .	691 „	17·45
Jejunal . .	585 „	37·77
Ileum . . .	412 „	67·65
Cæcum . .	80 „	94·34

The material obtained from the various fistulæ was of course mixed with the digestive juices. It is evident that the food material is practically completely absorbed by the time the lower end of the ileum is reached. The absorption takes place through the villi of the small intestine, partly directly into the blood stream, and partly by way of the lymphatic system, the food material in the latter case reaching the blood-vessels along the thoracic duct.

A *villus* is a finger-like projection of the mucous membrane, covered by columnar epithelium, each cell having a refractive, striated border on its free end, and resting by its deep extremity on a basement membrane. In the centre of the villus is a lymphatic vessel, the central lacteal, commencing by a blind extremity and communicating with the plexus of lymphatic vessels in the submucosa. Between the lacteal and the basement membrane are retiform tissue with scattered leucocytes, and strands of smooth muscle which extend from the muscularis mucosæ and are attached to both basement membrane and lacteal. A small artery is supplied to each villus and breaks up into a plexus of capillaries, lying immediately under the basement membrane and reuniting to form a small vein.

THE PROCESS OF ABSORPTION.

The absorption of the food products is effected by what, in the absence of a more precise definition, is called the vital activity of the epithelial cells of the intestinal mucous membrane. Experiments show that the process cannot be accounted for by filtration, diffusion, and osmosis. Filtration cannot take place, because the pressure in the blood capillaries of the mucous membrane is higher than the pressure in the lumen of the intestine. Again, a solution which is isotonic with the blood serum undergoes absorption, and an animal will even absorb its

own blood serum, so that diffusion and osmosis do not provide a complete explanation.

Although these physical processes do not account for absorption, they may nevertheless occur in the intestine. Thus, if the bowel contain a hypertonic solution of salt, water passes from the mucous membrane into the solution until the latter becomes isotonic with the blood, after which it is steadily absorbed. Osmosis may therefore retard, or on the other hand it may assist, absorption, but the passage of material from the lumen of the intestine into the villi must be regarded as due to the activity of the epithelial cells. If, however, the epithelial cells are injured by means of sodium fluoride, absorption is entirely regulated by the processes of diffusion and osmosis, and is therefore incomplete. Histological evidence as regards the absorption of fats shows that these substances pass through the epithelial cells, and experiments with dyes soluble in lipoids show that these also enter the cells themselves. The absorption of the products of protein digestion is also said to be accompanied by structural changes in the cells, and probably both amino-acids and dextrose pass through the cell substance. On the other hand, dyes insoluble in lipoids have been shown to pass between the cells, and the possibility of the intercellular cement forming a route for absorption cannot be considered to be absolutely excluded.

Generally speaking, therefore, absorption is an active or vital process, even in the case of water and salts, but it may be assisted or retarded by the physical processes of diffusion and osmosis.

The Absorption of the Products of the Digestion of Proteins.—The final stages of the digestive hydrolysis of the food proteins may take place in the mucous membrane of the intestine after absorption has begun. It has been shown that during the absorption of a protein meal the presence of peptone can be demonstrated in the wall of the bowel. If, however, the mucous membrane be kept at the body temperature for half an hour before it is analysed, no peptone will be found in it. Proteose and peptone may be taken up by the epithelial cells, and may be further hydrolysed by erepsin in the cells themselves with the formation of amino-acids. Even coagulable proteins may be taken up by the epithelial cells. It has already been pointed out that an animal can absorb its own serum, and this will take place when the intestine has been washed free of enzymes. Similarly egg-albumin may be absorbed, the amount introduced into the bowel being reduced by one-fifth in three hours. It is probable that, in these circumstances, complete digestive hydrolysis takes place in the mucous membrane, and that all food proteins are reduced to the amino-acid condition before being utilised in the body.

The protein derivatives are absorbed into the blood-vessels. After a protein meal the lymph which can be collected from the thoracic duct is not increased in amount, nor does it contain an increased quantity of protein. On the other hand, the absorption of a protein digest is not interfered with by ligature of the thoracic duct. It is, however, a matter of considerable difficulty to demonstrate the presence of amino-acids in the blood of the portal vein. Experiments which have been carried out show that a process of deamination takes place in the intestinal wall, whereby part of the amino-acids is oxidised, yielding ammonia and an oxy- or ketofatty acid, which pass into the portal circulation together with unchanged amino-acids.

The Absorption of the Monosaccharides.—The products of carbohydrate digestion all belong to the group of monosaccharides and are easily diffusible substances. The chief of these is dextrose, but some fructose is formed by the hydrolysis of cane sugar, and some galactose by that of the sugar of milk. All three varieties are absorbed directly into the blood stream. During absorption of a carbohydrate meal more sugar is found in the portal vein than in the hepatic vein. Moreover, the absorption of sugar is not accompanied by an increase of that substance in the lymph of the thoracic duct, and it is not interfered with by the ligature of that structure. Disaccharides are not absorbed from the intestine.

The Absorption of Fat.—The products of digestion of fat are fatty acid, held in solution by the bile salts, glycerol, and a little soap. The absorption of fat differs from that of amino-acids and dextrose in that it takes place for the most part into the lymphatic system. During the absorption of a fatty meal the lymphatics of the mesentery become filled with a milky fluid called *chyle*, so that they are easily visible to the naked eye. Chyle collected from the thoracic duct may contain over 6 per cent. of fat. Ligature of the thoracic duct diminishes, but does not entirely abolish fat absorption. The absorbed fat reaches the blood stream by the thoracic duct, and if an animal be bled during fat absorption, the plasma will be found to be milky from the quantity of minute fat globules present in it. A few hours later the plasma is again clear, because the small quantity of fat present in it is held adsorbed by the serum proteins, the remainder having either been oxidised or transferred to the fat depôts of the body.

About 98 per cent. of the fat taken as food is absorbed, but only 60 per cent. can be recovered in the chyle. The fate of the remaining 40 per cent. is unknown. It can neither be recovered from the blood nor from the thoracic duct, nor does it appear in the fæces.

The bile salts have an important influence on fat absorption, partly

because of their property of holding fatty acids in solution, and partly because they reduce surface tension and so facilitate the passage of the fatty material into the epithelial cells. In the absence of bile 60 per cent. of the fat of a meal remains unabsorbed. The absence of pancreatic juice also prevents the absorption of much of the fat, because fat is not absorbed unless it is acted on by lipase, and the lipase of gastric juice takes a comparatively small share in fat digestion.

The soaps formed in the intestine are split up by the intestinal epithelial cells into fatty acids and alkali. The fatty acids are absorbed and recombined with glycerol in the cells to form neutral fats.

Fat absorption may be studied histologically. During its occurrence the epithelial cells covering the villi become filled with droplets of fat, which may be stained black with osmic acid (fig. 125), red with Scharlach R or Sudan III, or blue by means of Nile blue. The droplets consist of neutral fat, so that a re-synthesis takes place in the epithelial cell, the bile salts which held the fatty acid in solution probably passing directly into the blood stream. The fat may be traced through the cell into the core of the villus, where the droplets are finely emulsified by the lymph in the tissue spaces, and are carried into the central lacteal. The wandering leucocytes in the villus take up fat droplets, and this may account to some extent for the 40 per cent. of absorbed fat which cannot be recovered from the thoracic duct.

Fig. 125.—Mucous membrane of frog's intestine during fat-absorption. (From Schäfer's *Essentials of Histology.*)

ep, epithelium; *str*, striated border; *c*, leucocytes; *l*, lacteal.

Alternate contraction and relaxation of the muscular fibres in the villus tends to propel the contents of the central lacteal towards the larger lymph vessels in the intestinal submucosa.

It has been demonstrated that hydrocarbons such as paraffin and petroleum are not absorbed in the intestine.

SECTION VI.

THE LARGE INTESTINE.

Four or five hours after each meal the contents of the small intestine begin to pass through the ileo-colic junction into the large intestine. An important factor in promoting the transference of

material from ileum to colon is the gastro-ileac reflex. The entrance of the succeeding meal into the stomach excites the production of peristaltic waves in the lower part of the ileum, each wave, as it reaches the ileo-colic junction, being followed by relaxation of the sphincter. In this way the contents of the ileum are propelled into the colon in successive portions, and if they contain bismuth the level which they attain in the ascending portion of the large intestine can be observed by means of X-rays to rise towards the hepatic flexure in an intermittent manner.

The material which thus passes into the large bowel is in the form of a jelly, coloured by the presence of bile pigment. It normally contains hardly any nutritive substances, the derivatives of the digestion of protein, fat, and carbohydrates having been almost completely absorbed in the small intestine. Indigestible substances contained in the food are present, especially cellulose, together with cast-off epithelial cells and the unabsorbed portions of the various digestive juices. The chief secretory waste products are the pigment of the bile, unabsorbed glycocholate and taurocholate of sodium, and cholesterol.

THE FUNCTIONS OF THE LARGE INTESTINE.

In carnivorous animals the large intestine is short, and its function is limited to the absorption of water and the consequent reduction in bulk of the fæces. In herbivora, on the other hand, the large intestine is of considerable length, and not only absorbs water but serves an additional purpose. A large proportion of vegetable food-stuffs consists of cellulose, which is not affected by the digestive enzymes. Cellulose is decomposed in the large intestine of the herbivora by bacterial action, being converted into fatty acids, which are absorbed and utilised in the body. Further, in all the higher animals, the cells lining the simple tubular glands of the large intestine are for the most part of the mucus-secreting type, and are of service in producing mucin, which acts as a lubricant and facilitates the passage of the fæces along the bowel.

In man the functions of the large intestine include secretion, excretion, and absorption, and in addition some bacterial decomposition takes place in its contents. (1) The *secreted* material, as in the higher animals generally, is mucin, derived from the tubular glands of the mucous membrane. (2) The substances *excreted* by the large intestine are calcium, magnesium, and iron, chiefly in the form of phosphates. The amount of calcium excreted by the bowel varies with the amount contained in the urine. Acid urine, such as occurs

normally in carnivora, and in man when the diet contains a due proportion of protein, holds calcium phosphate in solution, and in such a case the proportion of calcium excreted by the large intestine is relatively small. When the urine is alkaline, on the other hand, as in herbivora, and in man when the diet is largely vegetable, the amount of calcium excreted by the bowel is greater. Other chemical substances taken as drugs, for example mercury, may also be excreted by the large intestine.

(3) The only substance *absorbed* in any quantity in the large bowel is water. The contents of the ascending colon contain no nutritive substances, but their bulk is fairly large owing to the amount of fluid which they contain. During their stay in the large intestine the bulk is greatly reduced, chiefly by the absorption of water. It is said that 400 c.c. are absorbed from the contents of the colon in twenty-four hours. The possibility of the absorption of nutritive substances in the large intestine is of importance, because attempts are frequently made to introduce food-stuffs into the body by means of rectal injections. Experiments prove, however, that nutritive material is not absorbed by the large intestine, with the exception of small amounts of dextrose, which are too minute to be of real practical value.

(4) The *bacteria* in the human large intestine act upon cellulose with the production of lower fatty acids, marsh gas (CH_4), carbonic acid, and hydrogen. Undigested protein residues also undergo bacterial decomposition with the production of the aromatic bodies, indol (C_8H_7N), skatol (methyl-indol), and phenol. It is possible that the fatty acids derived from cellulose may be absorbed, as they are in the herbivora, and there is evidence that absorption of indol, skatol, and phenol takes place, inasmuch as compounds of these substances with sulphuric acid, the ethereal sulphates, are found in the urine.

THE FÆCES.

The residues which finally reach the rectum constitute the fæces, and form a solid or semi-solid mass, coloured by the pigment stercobilin, which is derived from bilirubin. The composition of the fæces has already been indicated. They contain about 65 per cent. of water, with organic material and inorganic salts. The organic substances are partly nitrogenous, and partly of a fatty nature and soluble in ether. The nitrogenous constituents include cholic acid, dyslysin, indol and skatol, purin bodies, epithelial cells, and dead bacteria. The lipoids are fatty acids, lecithin, and coprosterin, a body allied to

cholesterol. There may be a small quantity of neutral fat. When vegetable food has been taken, the fæcal matter will include undecomposed cellulose, but, for the most part, the fæces consist of substances derived from the digestive tract itself.

THE MOVEMENTS OF THE LARGE INTESTINE.

The movements of the large intestine have been most satisfactorily studied with the aid of X-rays (fig. 126).[1] The cæcum and ascending colon are filled, in the manner which has already been described, by the peristaltic contractions of the ileum, and are entirely passive during the process. Later, segmental contractions occur in this part of the bowel, similar in nature to those which take place in the small intestine. These movements tend to mix the contents and promote the absorption of water. The transference of the fæces from the cæcum and ascending colon to the transverse and descending colon takes place at long intervals, usually three or four times in twenty-four hours, by means of peristaltic contractions. These movements generally follow the entry of food into the stomach, and are ascribed to a gastro-colic reflex. Scattered masses may remain in the transverse colon for a time, and these are suddenly transferred to the descending colon by a peristaltic wave.

The fæces remain for a time in the sigmoid flexure, until, usually after a meal, a certain amount passes into the rectum and gives rise to the desire for defæcation. By relaxation of the sphincter ani, accompanied by contraction of the walls of the sigmoid flexure and rectum assisted by contraction of the voluntary muscles of the abdominal wall and pelvic floor, the lower end of the bowel is evacuated. The act is a reflex one, but in the adult it is under the control of the higher centres.

The Nerve Supply of the Large Intestine.—The large intestine receives its nerve supply from the sympathetic system and from the pelvic visceral nerves or *nervi erigentes*. The sympathetic fibres form the inferior mesenteric nerves, running from the inferior mesenteric ganglion to the ascending, middle, and transverse colon, and the hypogastric nerves pass from the same ganglion to the rectum. The preganglionic fibres emerge from the spinal cord by the second, third, and fourth anterior lumbar nerve roots.

The nervi erigentes emerge from the cord by the second and third sacral nerve roots, and are distributed to the whole length of the large

[1] We are indebted for this diagram to the kindness of the Oxford University Press.

intestine. Stimulation of the sympathetic nerves causes inhibition of the tone of the intestinal wall and cessation of the rhythmic movements. Stimulation of the nervi erigentes causes contraction of the whole length

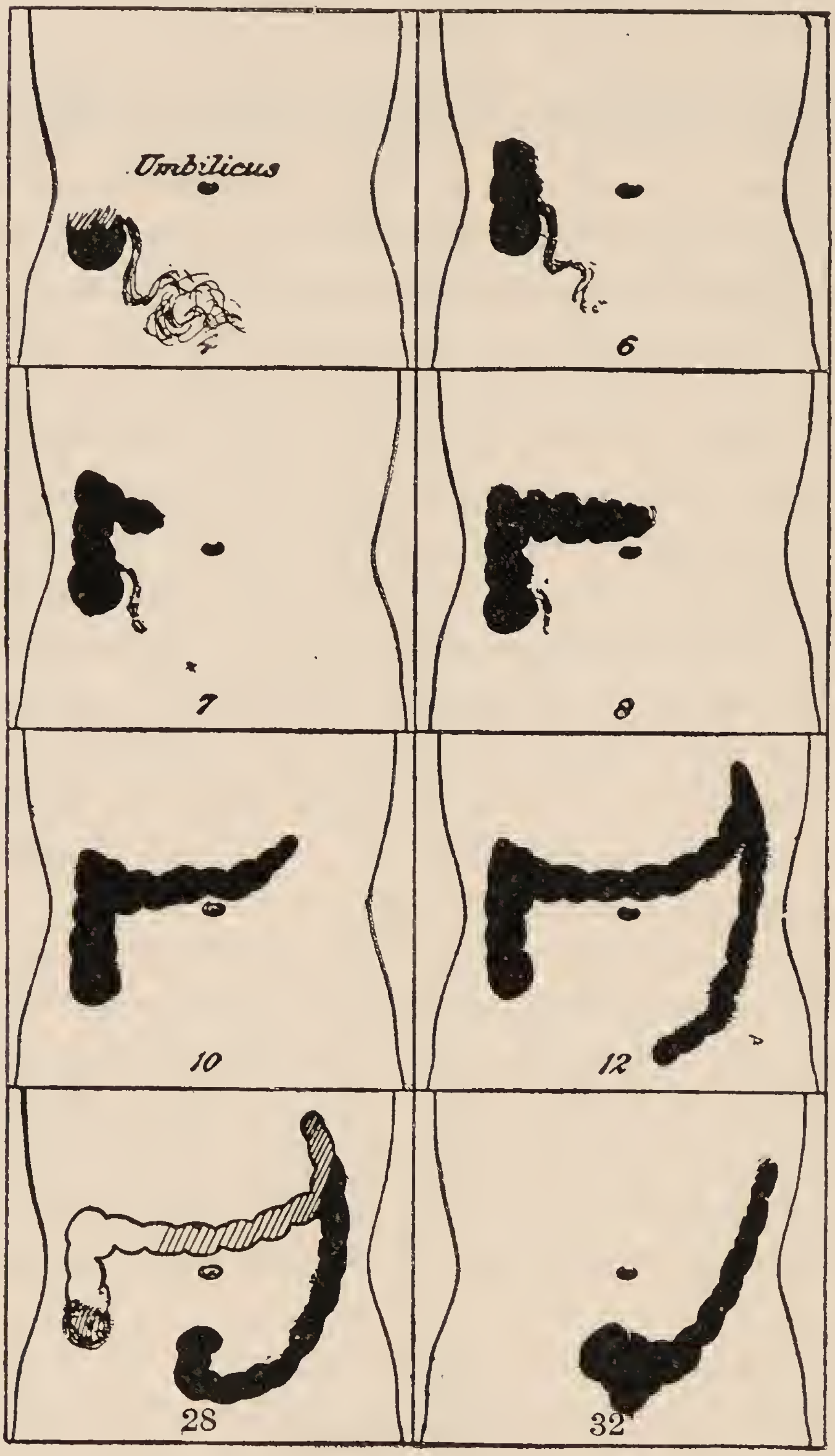


Fig. 126.—Passage of food along the large intestine after a bismuth meal, as seen by means of X-rays. The numbers refer to the hours after the meal was taken. (Hertz.)

of the colon. The sympathetic is therefore inhibitory and the pelvic visceral nerves are motor in function.

As in the small intestine, there are ganglionated plexuses in the intestinal wall, of which the myenteric, lying between the layers of the muscular coat, is associated with the local reflex mechanism controlling the movements of the bowel.

THE VERMIFORM APPENDIX (VERMIFORM PROCESS).

In man the cæcum is very short and has attached to it a wormlike process, the vermiform appendix. This has a thin muscular coat and a thicker mucous coat, the latter composed almost entirely of lymphoid tissue containing scattered tubular glands. The human appendix is regarded as a vestigial remnant of no functional importance. It is homologous with the long and capacious cæcum of herbivora, which serves the useful purpose of retaining food material while the cellulose undergoes bacterial decomposition.

CHAPTER XI.

METABOLISM.

SECTION I.

THE food-stuffs, after being digested and absorbed into the blood or lymph, are carried to the tissues, in which they pass through a series of complex chemical transformations, the end products of which leave the tissues and are removed from the body by the lungs and kidneys. This series of chemical changes constitutes *metabolism*, and the metabolic activities of the tissues are of two kinds. On the one hand, the living tissues are constantly undergoing changes whereby a portion of their substance is broken down and removed from the body; on the other hand, this loss is replaced by the building up of fresh tissue from the nutritive materials supplied in the blood. The former of these processes is called *katabolism*, and the latter *anabolism*.

These changes involve the consumption of a large amount of oxygen, and the evolution of energy in the form of heat and muscular work. The food-stuffs are protein, fat, and carbohydrate, 90 to 94 per cent. of those consumed on an ordinary diet being absorbed into the blood stream, and the remainder being lost in the fæces. The fats and carbohydrates are completely converted into carbonic acid and water, and the proteins partly into carbonic acid and water, the nitrogen being excreted as urea and other incompletely oxidised substances in the urine. The carbonic acid is removed from the body almost entirely through the lungs, and the water by the lungs, kidneys, and skin. The changes undergone by the food-stuffs in the body may, therefore, be studied in three ways, namely (1) by measuring the total amount of heat evolved in their oxidation, (2) by determining the quantity of oxygen required for the carrying out of these oxidations, and (3) by measuring the amount of the end products which are formed. We may also attempt to follow out the series of changes taking place in the individual food-stuffs in the tissues themselves.

THE PRODUCTION OF HEAT.

The heat evolved by the complete oxidation of a food-stuff can be ascertained by means of the bomb calorimeter (fig. 127), which consists of a metal bomb, A, through the top of which pass two wires, h and h', connected by a strip of soft iron wire; one gram of the substance, *e.g.* dextrose, which is to undergo combustion, is placed in contact with the iron wire. The bomb is filled with oxygen from an oxygen cylinder, under a pressure of 7 to 8 atmospheres, and is enclosed in a bath, C, containing a known volume of water, which is surrounded by an air and a water jacket, D. When a current is passed through the wires the soft iron fuses and ignites the sugar, which is rapidly oxidised to carbonic acid and water. The heat evolved in this process raises the temperature of the water in which the bomb is placed; and if the temperature of the water before and after the combustion is observed, the amount of heat evolved can be calculated, and is expressed in *calories*. A large calorie is the amount of heat required to raise 1000 grams of water 1° C. (A small calorie is the amount of heat necessary to raise the temperature of 1 gram of water 1° C.; this measurement is now seldom used.) If the volume of water in such an experiment is 1 litre and the rise of temperature is 4°·1 C., 1 gram of sugar when fully oxidised gives out 4·1 calories; and this amount, which is spoken of as the calorie value of dextrose, is constant. The average calorie value of fat, carbohydrate, and protein is shown in the following table:—

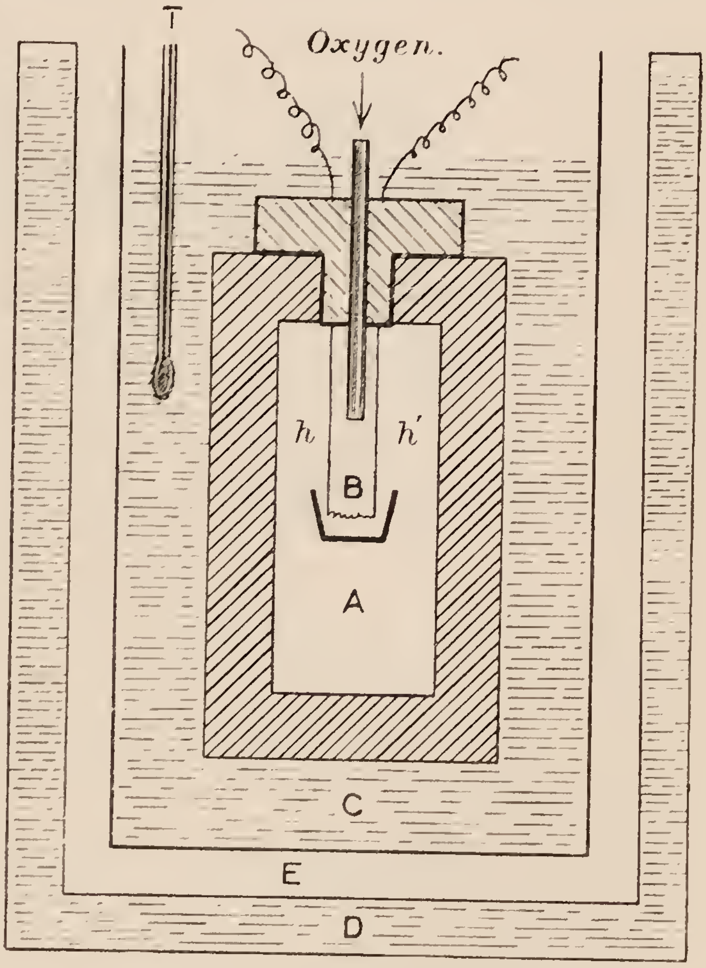


FIG. 127.—Bomb calorimeter.
T = thermometer: E = air jacket; B = strip of iron wire.

Fat, 1 gram = 9·3 calories.
Carbohydrate, 1 gram = 4·1 calories.
Protein, 1 gram = 4·1 calories.

The calorie value of protein when completely oxidised in the calorimeter is 5·6; but protein is not fully oxidised in the body, its nitrogen

being excreted in the urine largely as urea, and to a less extent as other substances, each of which has a calorie value of its own. In determining the physiological calorie value of protein, the heat value of urea and other nitrogenous products must be deducted from the figure 5·6. When this is done, the heat value of protein is reduced to 4·1, which represents its calorie value in the body. The energy set free in the body by the oxidation of the food-stuffs appears partly as heat and partly as muscular work. The energy set free as muscular work may be calculated as heat according to the following equation:—

425 gram-metres of work = 1 calorie.

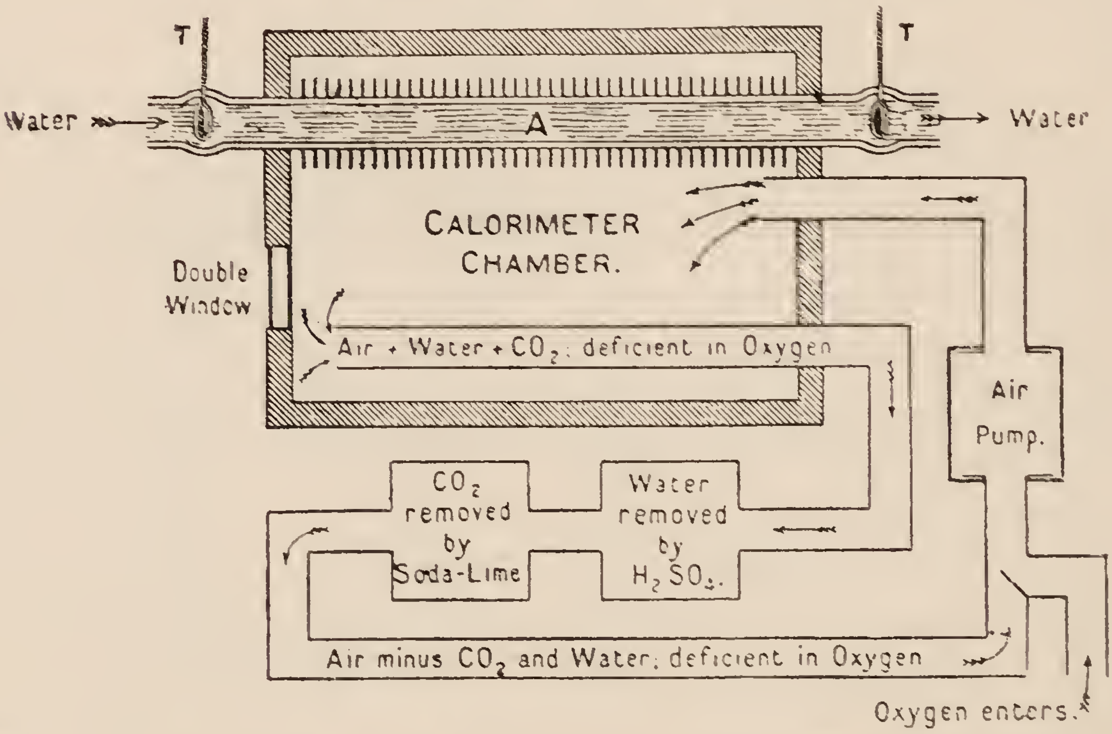


FIG. 128.—Diagram to show the principle of the Atwater-Benedict calorimeter. (After Halliburton.) Starling's *Principles of Physiology*.

The heat formed in the body is determined by placing the animal in a suitable calorimeter. Large calorimeters such as that of Atwater and Benedict have been constructed, in which a man can live for two or three days, or longer, and can carry out muscular work. The Atwater-Benedict calorimeter consists of a room, with double, non-conducting walls, containing a series of pipes through which water is flowing at such a rate that the temperature of the room remains constant (fig. 128). The whole of the heat given off by the man warms the water passing through the pipes, and is thus carried off. By measuring the amount of water flowing along the pipes and the rise in its temperature as it passes through the calorimeter, the heat evolved by the individual can be estimated. By means of these methods it is possible to determine, on the one hand, the energy supplied to the body in the food, and, on the other hand, the energy lost from the body as heat and muscular work. It is found that these two

balance one another within the limits of experimental error, and that the energy lost from the body has its origin entirely in the potential energy taken into the body in the food. Thus the principle of the conservation of energy is as true for living beings as it is in the rest of the organic and the inorganic world.

Day of Experiment.	Calorie Value of Material Oxidised in the Body.	Calories Lost from the Body.
1	2349	2414
2	2345	2386
3	2391	2413

THE RESPIRATORY QUOTIENT AND EXCHANGE.

The *respiratory exchange* is the total quantity of oxygen taken into the body and of carbonic acid discharged from the body in a given time.

The respiratory quotient, as already mentioned (p. 250), is the *ratio* of the amount of carbonic acid discharged from the body to the amount of oxygen taken in in a given time.

In man the amount of oxygen used and of carbonic acid evolved in the metabolic changes taking place in the body under varying conditions, such as rest or muscular exercise, can be determined by means of the calorimeter just described. The air leaving the calorimeter passes through vessels containing soda lime, which absorbs carbonic acid, the increase in weight of these vessels giving the weight of carbonic acid exhaled in a given time. The oxygen used by the individual is replaced from a cylinder, the amount supplied being measured. A continuous circulation of air through the chamber is provided by a small pump.

The respiratory quotient and exchange may also be determined approximately by finding with the aid of a spirometer the average volume of air breathed in a minute, and by analysing a sample of expired air. Thus, if a man breathes 500 c.c. of air at each breath and his respirations are 16 per minute, he breathes 8 litres per minute. Assuming that the expired air contains 16 per cent. oxygen and 4 per cent. carbonic acid, he must have absorbed 5 c.c. oxygen from each 100 c.c. of air breathed, namely 400 c.c.; similarly, he must have breathed out 320 c.c. carbonic acid, and the respiratory quotient is $\frac{320}{400} = 0{\cdot}8$.

For small animals the apparatus devised by Haldane and Pembrey,

and shown in fig. 129, may be employed. The animal, *e.g.* a mouse or guinea-pig, is placed in a vessel through which is drawn a current of air, freed from carbonic acid and water by passing it through soda lime and sulphuric acid. The water in the air leaving the chamber is absorbed by pumice saturated with sulphuric acid, in the tubes B B; these are weighed before and after the experiment, the increase in weight representing the water given off by the animal. The carbonic acid evolved is absorbed in the tube, which contains soda lime, and the water taken up from the soda lime is absorbed by sulphuric acid; these two tubes are weighed before and after the experiment. The amount of oxygen taken up by the animal is determined indirectly by subtracting

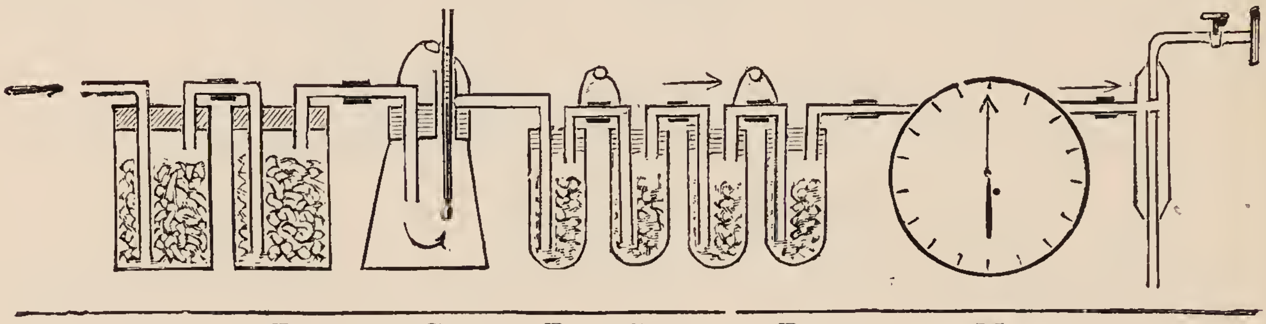


FIG. 129.—Haldane-Pembrey respiration apparatus for mouse. (From *Practical Physiology*, by Pembrey and others.)
A, soda lime; B, H_2SO_4; C, chamber for animal; M, gas meter.

the loss in weight of the animal during the experiment from the total weight of carbonic acid and water given off.

The respiratory exchange serves as an index of the total oxidative processes taking place in the body, just as the amount of oxygen used, and carbonic acid evolved, by a single organ indicate the functional activities of that organ. It is not influenced by the nature of the food which is consumed, but is very greatly modified by the functional activity of the animal. During exercise the chemical changes taking place in muscle are increased, heat is evolved, and more oxygen is used in the body; since the muscles form about 40 per cent. of the total weight of the body, the respiratory exchange during exercise may be eight to ten times greater than during rest.

RESPIRATORY EXCHANGE IN MAN. (BENEDICT AND CATHCART.)

	Oxygen Absorbed in c.c. per Minute.	Carbonic acid Discharged in c.c. per Minute.
Resting . .	242	218
Moderate work .	1490	1224
Severe work .	1850	1789

Further, the respiratory exchange varies with the size of the animal. The smaller the animal the greater is its surface relatively to its weight, and since the body loses heat chiefly from its surface, the relative loss of heat must be greater in a small than in a large animal. In order to make up for this loss the smaller animal must produce a relatively larger amount of heat, and must use up in this process relatively more oxygen, than a bigger animal. It is found, in fact, that metabolism is more active and the respiratory exchange is greater, weight for weight, in small animals than in large ones.

Apart from the question of size, the consumption of oxygen is also relatively greater in growing than in adult animals, since oxygen is being used not only in the chemical changes necessary to maintain the weight of the animal, but also in the metabolic processes associated with growth.

The Respiratory Quotient.—The size of the respiratory quotient is determined almost entirely by the character of the food consumed by an animal. If an animal were living solely upon carbohydrate food, all the oxygen taken into the body would reappear as carbonic acid, and the quotient would be 1, in accordance with the following equation:—

$$C_6H_{12}O_6 + 6O_2 = 6CO_2 + 6H_2O. \quad \frac{6CO_2}{6O_2} = 1.$$

If the diet consisted entirely of fat, the oxygen taken into the body would not all reappear as carbonic acid; some of it would be used in converting hydrogen into water, and the quotient would be less than 1, the oxidation being represented thus:—

$$\underset{\text{Olein.}}{C_3H_5(C_{18}H_{33}O_2)_3} + 80O_2 = 57CO_2 + 52H_2O. \quad \frac{57CO_2}{80O_2} = 0{\cdot}71.$$

On a purely protein diet part of the oxygen would be combined with nitrogen and sulphur, as well as with hydrogen, and the respiratory quotient would be approximately 0·8. In man living on a mixed diet the quotient is usually about 0·85, and can be lowered by the exclusion of carbohydrate, or raised when the diet consists mainly or exclusively of carbohydrate food. The respiratory quotient is thus of great value, in that it gives an indication of the nature of the food which is being oxidised in the body under various conditions. During muscular exercise, for example, the quotient rises very slightly, and it is evident that the active muscle uses a rather larger proportion of carbohydrate than resting muscle. In a large number of experiments made on the same individual, the average respiratory quotient was 0·85 during rest, and 0·88 during muscular exercise.

END PRODUCTS OF METABOLISM.

The whole of the carbon in fat and carbohydrate, and a large proportion of that in protein, is removed from the body in a completely oxidised form as carbonic acid, while the nitrogen of protein leaves the body in the form of urea, uric acid, and other substances, which are excreted in the urine. Since protein contains about 16 per cent. nitrogen, it is possible, by determining the total amount of nitrogen in the urine, to calculate the amount of protein from which it has been derived; each gram of nitrogen in the urine represents the breaking down in the body of 6·3 grams of protein. By measuring the output of nitrogen in the urine and the amount of carbonic acid discharged from the lungs daily, the total amount of protein, fat, and carbohydrate which has been oxidised in the body can be calculated, if the respiratory quotient is known. In health the amount of carbon and nitrogen thus removed from the body is equivalent to the amount taken in with the food, provided that the weight of the individual remains steady. If the individual is putting on weight, some of the carbon taken in the food is retained in the body as fat or carbohydrate; when weight is being lost, more carbon, and possibly more nitrogen, will be discharged than are taken in with the food.

We may now consider the changes taking place in the various foodstuffs after their absorption from the digestive tract.

SECTION II.

THE METABOLISM OF FAT.

The fats taken by the mouth, after being hydrolysed in the digestive tract and re-synthesised in the walls of the villi, enter the thoracic duct as neutral fats and pass into the blood stream. For a short time after a fatty meal the fats circulate in the blood stream, and may give the blood a slightly milky appearance, but they are rapidly taken up and stored in the subcutaneous tissues and omentum, which serve as depôts in which the fat not immediately required by the body can be kept. The composition of the subcutaneous fat thus reflects that of the fat in the food; and if abnormal and easily recognisable fats are given by the mouth, they can be identified shortly afterwards in the fat in the subcutaneous tissue. For this purpose, erucic acid or fats containing iodine may be used. In man the greater part of the fat deposited in the body is derived from the fat in food, but it can be formed, and in herbivora is mainly formed, from carbohydrates. This

was demonstrated in the classical experiment of Lawes and Gilbert. These observers took two young pigs from the same litter. One was killed, and the amount of fat and protein in its body was determined; the other was fed on a diet containing known quantities of protein, fat, and carbohydrate, and after some weeks it was killed, and the amount of fat in its body was ascertained.

After deducting the amount of fat taken in the food from that present in the animal's body when it was killed, a large residue remained, which must have been formed either from the protein or carbohydrate of the food. It could not have been formed from protein, since the amount of fat in the animal was larger than the amount of protein food consumed. The greater part of the fat must, therefore, have been formed from carbohydrate; and there is no doubt that in herbivora, whose diet consists mainly of carbohydrate, the bulk of the fat is formed in this way. There is no evidence that fat can be formed from protein, and animals, *e.g.* dogs, fed on a purely protein diet do not put on any fat.

The process by which carbohydrate is converted into fat in the body is not known, but it is probable that the carbohydrate is first broken down into some simple substance such as acetic aldehyde ($CH_3 . CHO$), or pyruvic acid ($CH_3 . CO . COOH$), which are known to be formed from carbohydrate, and that by the linking up of molecules of these bodies the fatty acids are synthesised.

Their possible formation from aldol is thus shown:—

$$(1)\quad CH_3 . CHO + CH_3 . CHO = CH_3 . CHOH . CH_2 . CHO \text{ (aldol)}$$

$$(2)\quad CH_3 . CHOH . CH_2 . CHO + \begin{matrix} H \\ H \end{matrix}\!\!>\!O = \underbrace{CH_3 . CH_2 . CH_2 . COOH}_{\text{Butyric acid.}} + H_2O$$

The fat formed from carbohydrate contains a large proportion of stearin and palmitin, and has a higher melting point than that usually deposited in the tissues from the food. For this reason the fat of cattle is much firmer than that of omnivorous animals, which may be practically fluid at the body temperature.

The fat in the fat depôts cannot be used directly by the muscles or other tissues, but has first to undergo certain changes in the liver; these consist in the conversion of saturated into unsaturated fats by the removal of hydrogen. A saturated fat, *e.g.* stearin, is one in which the affinities of all the carbon atoms are satisfied, whereas an unsaturated fat, such as olein, is one in which the affinities of two or more of the carbon atoms are unsatisfied and the carbon atoms are united by a double bond.

Thus oleic acid has the formula, $C_8H_{17} . CH : CH . C_7H_{14} . COOH$, and has one double bond.

The fatty acids present in the liver contain two, three, or even four double bonds, each of which represents a weak spot in the long chain of carbon atoms; and an unsaturated fatty acid tends to split at these points with the formation of smaller molecules. The unstable fatty acids formed by the liver are carried to the muscles and other tissues, in which they enter the complex protoplasm of the living cells, and are finally oxidised to carbonic acid and water.

During starvation the fat in the body is used by the tissues as their chief source of energy: the liver receives more fat than usual from the fat depôts, and is called upon to desaturate fat in larger amount and thus render it available for use by the tissues. The fat passes to the liver from the fat depôts more rapidly than it can be desaturated, and an accumulation of saturated fat takes place in the liver; this accumulation, which is termed *fatty infiltration*, readily occurs in starvation and equally readily passes off again when food is given. It takes place, not only in starvation, but whenever the tissues need a larger supply of fat, for example in diabetes.

The nature of the process whereby the subcutaneous tissues and omentum take up fat after a meal and give it off to the blood again in times of need is not known, though it has been supposed to be due to the reversible action of an enzyme (lipase) in the fat cells.

In a man whose weight remains steady the fat taken in the food is rapidly used in supplying energy in the body, and little or none of it is permanently stored in the fat depôts. When weight is being put on, a certain proportion of fat in the food is stored up instead of being oxidised, and fat may also be formed from carbohydrate. On the contrary, loss of weight during starvation, or produced by some other means, involves depletion of the store of fat in the body. The fat normally stored represents a reserve of potential energy which can be increased, or which in time of need can be drawn upon for the use of the muscles and other tissues; and owing to its high calorie value, the energy which may be thus kept in reserve is very considerable.

The fats on leaving the liver pass to the tissues, in which they become combined in such a way that they can no longer be recognised histologically, although their presence is made manifest by chemical analysis of the tissue. A healthy kidney, for instance, when stained with Sudan III may show only a few specks of fat here and there, although when analysed it is found that 18 to 20 per cent. of its dried substance is fat. Under the influence of certain poisons (*e.g.* phos-

phorus), and in some diseases, the combination of fat with the rest of the protoplasm is broken, and the fat is set free in such a form that it can be stained and recognised under the microscope. This change, which is called *fatty degeneration*, was formerly believed to be the result of the formation of fat from protein. Chemical analysis of such an organ shows, however, that it contains no more fat than would be found in a healthy organ. Hence fatty degeneration implies, not the formation of fat from protein, but merely the setting free in a visible form of previously combined fat.

The fat is normally completely oxidised in the tissues to carbonic acid and water; the nature of the changes taking place is not fully understood, but in all probability the long chain of carbon atoms constituting a fatty acid is broken down in stages, two carbon atoms being split off at each stage. The complete oxidation of fat, however, is dependent upon the presence of carbohydrate in the tissue cells.

Acidosis.—When the tissues are deprived of carbohydrate, for example during starvation or on a diet free from carbohydrate, the oxidation of fat is incomplete, and intermediate metabolic products are formed in the tissues and pass into the blood and urine. These products are β-oxybutyric acid, aceto-acetic (diacetic) acid, and acetone, their chemical relationship being shown as follows:—

$$\begin{array}{ccccc} CH_3 & & CH_3 & & CH_3 \\ | & & | & & | \\ CHOH & & CO & & CO \\ | & \rightarrow & | & \rightarrow & | \\ CH_2 & & CH_2 & & CH_3 \\ | & & | & & \\ COOH & & COOH & & \end{array}$$

β-oxybutyric acid — Aceto-acetic acid — Acetone

There is evidence that β-oxybutyric acid and aceto-acetic acid are normally formed in the body during the metabolism of fat, but are fully oxidised; in the absence of carbohydrate they pass into the blood stream, and aceto-acetic acid, instead of undergoing oxidation, is converted into acetone. The origin of these bodies from fat is clearly shown by the observation that when the diet consists solely of fat their amount in the urine may become very large. β-oxybutyric acid and its products are formed to some extent at least in the liver.

The presence of these substances in the blood and urine is known as *acidosis*, and is an indication, whenever it occurs, that the supply of carbohydrate to the tissues is inadequate. In the blood β-oxybutyric acid and diacetic acid combine with ammonia which would otherwise

be converted into urea, and in acidosis the amount of ammonia excreted in the urine is increased. By this means the acids are neutralised and the reaction of the blood remains unchanged: and the amount of ammonia in the urine serves as an index of the extent to which these acids are being formed in the body.

Test for Acetone in Urine.—A few c.c. of urine are saturated with ammonium sulphate, and a few drops of ammonia are added; on the addition of a drop or two of a freshly prepared solution of sodium nitro-prusside a beautiful purple is slowly produced, which varies in depth with the amount of acetone present and fades after a short time. No other substance gives this test, which is called Rothera's test.

Test for Diacetic Acid in Urine.—On adding a solution of ferric chloride, in excess of that required to precipitate the phosphates, the appearance of a deep red colour indicates the presence of diacetic acid.

There is no simple test for β-oxybutyric acid.

Since carbohydrate is readily converted into fat in the body, it might be expected that the converse change would also occur. There is no definite evidence, however, that fat is converted into carbohydrate, except perhaps in hibernating animals, in which the respiratory quotient is extremely low and may be 0·3 or 0·4.

Such a quotient could occur if fat were being transformed into dextrose, since, in this process, oxygen would be taken into the body which would not reappear as carbonic acid.

SECTION III.

METABOLISM OF CARBOHYDRATE.

The carbohydrates are absorbed from the digestive tract and enter the blood stream mainly as dextrose, and to a small extent as fructose and galactose. The arterial blood, when examined, is found to contain 0·1 to 0·2 per cent. of dextrose, and this amount is not increased after a carbohydrate meal, even though in such circumstances 100 grams or more of sugar may be rapidly absorbed from the digestive tract into the portal blood. The sugar in the portal blood, however, does vary in amount, being slightly less than that in the general circulation during starvation, and distinctly greater after a carbohydrate meal: and it is clear that the sugar absorbed during digestion undergoes some change as the blood passes through the liver. This change consists in the conversion of sugar into *glycogen*, which is stored in the liver cells.

Preparation of Glycogen.—An animal is killed a few hours after a meal rich in carbohydrate, and the liver is rapidly excised, chopped into small pieces, and thrown into boiling water. After two or three minutes the pieces of liver are taken out of the water, ground up with

sand, and returned to the boiling water, which is made slightly acid with acetic acid. The mixture is boiled for a minute or two and is then filtered; the coagulated proteins remain behind, and the filtrate, which is free from protein, forms an opalescent solution containing glycogen.

Glycogen, like dextrin, gives a mahogany-brown colour with iodine, and does not reduce Fehling's solution; when boiled with dilute mineral acids it is converted into dextrose. It differs from dextrin, first, in forming an opalescent solution, whereas a solution of dextrin is clear, and, secondly, in being precipitated more readily by alcohol. Further, glycogen is precipitated by basic lead acetate, which does not precipitate dextrin.

If the liver is left for some hours before being treated in the manner just described, the filtrate contains an abundance of dextrose, but no glycogen. The amount of glycogen present in the fresh liver varies with the previous condition of the animal and, if it has been well fed, may form 10 per cent. of the total weight of the liver. When an animal has been starved for a few days, and particularly if during this period it has been made to take exercise, the liver may be almost free from glycogen. Both in the well-fed and in the starved animal the percentage of sugar in the arterial blood remains unaltered. These observations can be confirmed by histological examination of the liver. When the liver of a well-fed animal is hardened in alcohol and examined microscopically, the cells are seen to be full of glycogen, which can be stained with iodine; and the protoplasm may be reduced to a network in the meshes of which the glycogen lies. An examination of the liver of a starved animal shows that glycogen is almost or quite absent.

From these and other observations Claude Bernard, who discovered glycogen, concluded, first, that the sugar absorbed from the digestive tract entered the portal blood, and that, as it passed through the liver, this organ removed the sugar from the blood and stored it as glycogen. Secondly, he believed that the percentage of sugar in the systemic blood normally remained constant, and that as the sugar was removed from the blood by the tissues for their metabolism some glycogen was made into sugar by the liver: this passed into the general blood stream, thereby keeping the percentage of sugar in arterial blood at the normal level. He regarded the rapid conversion of glycogen into sugar after death as being due to a ferment, the activity of which was no longer controlled, as it had been during the life of the animal. This view has been generally accepted, and glycogen may be regarded as a store of carbohydrate which is increased at each meal, and which is continuously being drawn upon by the tissues. In all probability the conversion of glycogen into sugar, and of sugar into glycogen, is carried out by a

reversible ferment. We may perhaps regard glycogen as a sort of current account, which fluctuates from day to day, whereas the store of fat in the body represents a more permanent reserve, or capital account, which can be called upon in times of stress.

Although the main source of glycogen is carbohydrate food, it can also be formed to some extent from protein, since, when an animal is starved until its liver is presumably free from glycogen, and is then killed shortly after a large meal of protein, some glycogen is found in its liver. There is no evidence that glycogen can be formed from fat.

Glycogen is found most abundantly in the liver, but it occurs in muscles, being especially plentiful in fœtal muscles, and it is also present in the white blood corpuscles.

FATE OF SUGAR.

The carbohydrate taken into the body ultimately undergoes one of two changes. Some of it, more particularly in herbivora, is converted into fat; the remainder passes from the blood to the tissues, where it is oxidised and used as a source of energy. There is direct evidence that sugar is made use of by the tissues. Using the heart-lung preparation (p. 199), Starling found that the normal heart used up sugar at the rate of about 4 milligrams per gram of heart per hour. Further indirect evidence to the same effect is furnished by the fact that the glycogen disappears most rapidly from the liver when the functional activity of the tissues is greatest. Thus severe muscular exercise or the convulsions induced by strychnine lead to the rapid disappearance of glycogen from the liver. Neither the conditions which determine the taking up of sugar by the tissues from the blood, nor the intermediate stages in its oxidation are fully known, but it is probable that lactic acid is an intermediate product in the conversion of sugar into carbonic acid and water.

Some light is thrown on the conditions which influence the setting free of sugar from the liver and its further oxidation in the tissues by certain abnormal conditions in which sugar appears in the urine, and which are known as glycosuria.

Glycosuria.—The urine normally contains slightly less than 0·1 per cent. of dextrose, and does not reduce an alkaline solution of copper sulphate; the term glycosuria is only used when the urine contains dextrose in sufficient amount definitely to reduce such a solution. This may occur in a variety of circumstances. If dextrose is injected into the circulation or under the skin, the percentage in the blood rises (hyperglycæmia), and the sugar is at once excreted by the kidneys. A similar condition, known as (1) *Alimentary Glycosuria*, is observed

when very large amounts of sugar are taken by the mouth. The ingestion of starch, even in large quantities, does not lead to glycosuria, since its digestion and absorption are sufficiently slow to enable the liver to convert the sugar into glycogen.

(2) *Adrenalin Glycosuria.*—The injection of a small quantity of adrenalin into the circulation is followed by the appearance of dextrose in the urine; at the same time, glycogen disappears from the liver, and the percentage of sugar in the blood is increased. Evidently the adrenalin causes the liver to discharge its glycogen into the blood as sugar, which is excreted by the kidneys. Glycosuria may also occur under any conditions in which adrenalin is set free into the blood stream in larger amount from the suprarenal glands.

(3) *Diabetic Puncture.*—Claude Bernard was the first to show that puncture of the floor of the fourth ventricle in rabbits is followed by hyperglycæmia, glycosuria, and the disappearance of glycogen from the liver; if the animal has been previously starved to rid its liver of glycogen, glycosuria does not follow the puncture. This experiment was regarded by Bernard as a further proof of his theory as to the function of glycogen in the body. The diabetic puncture fails to produce glycosuria after division of the splanchnic nerves or removal of the suprarenal glands, and in all probability the puncture stimulates the medulla oblongata in such a way that adrenalin is set free into the circulation and causes glycosuria.

(4) *Phloridzin Glycosuria.*—Phloridzin is a glucoside, which on hydrolysis yields glucose and phloretin. A small amount of phloridzin or phloretin, when injected into an animal, produces glycosuria and the disappearance of glycogen from the liver; but phloridzin glycosuria differs from that just described in that the percentage of sugar in the blood is not increased, but tends rather to be diminished. Phloridzin acts upon the cells of the renal tubules, causing the kidneys to excrete dextrose, even when the percentage of the latter in the blood is not raised. That it acts upon the kidneys may be shown by collecting the urine separately from the two kidneys, and injecting a small dose of phloridzin into one, *e.g.* the right, renal artery; the urine flowing from the right kidney is then found to contain sugar some time before it appears in the urine from the opposite kidney. Phloridzin appears to act directly upon the cells of the renal tubules, stimulating them to secrete sugar from the blood, and this view is supported by the observation that the repeated administration of phloridzin produces definite histological changes in the cells of the renal tubules.

When repeated doses of phloridzin are given to an animal, the glycosuria persists after the glycogen has disappeared from the liver,

and even when the animal is not receiving carbohydrate food. The sugar in this case is not derived from carbohydrate, but is formed from protein; this is shown by the fact that in a starving animal the ratio of the amount of dextrose in the urine to that of nitrogen, expressed as $\frac{D}{N}$, becomes constant, varying in different animals from 2·5 to 3·5. Owing to the energy lost to the body as sugar, the tissues are compelled to use an excessively large amount of protein as a source of energy, and the rapid disintegration of protein increases the output of nitrogen in the urine, the animal wastes, and its condition resembles that seen in severe diabetes.

(5) *Experimental Diabetes.*—Von Mering and Minkowski were the first to discover that the complete removal of the pancreas in dogs and other animals is followed in a few hours by glycosuria, which soon becomes very severe. The animals waste rapidly, the urine contains β-oxybutyric acid and acetone, as well as dextrose, and death occurs in one to two weeks. During life the urine contains an excess of sugar, and after death the liver is found to be almost free from glycogen. These symptoms are not due to the absence of the pancreatic juice from the digestive tract, since ligature of the pancreatic duct does not lead to glycosuria. Nor do they occur if a small portion, one-tenth or more, of the pancreas is left in the body, although the subsequent removal of this fragment is followed by the train of symptoms just described. In diabetic animals the respiratory quotient is low, and from this it has been inferred that the muscles and other tissues are unable to make use of and to oxidise the sugar supplied to them in the blood, with the result that hyperglycæmia occurs and sugar is excreted by the kidneys.

Further, it is generally assumed that the pancreas furnishes an internal secretion, that is to say, some substance which passes directly into the blood stream, and which links the sugar to the tissue cells; in the absence of this link the tissues are unable to take up sugar and therefore cannot oxidise it.

This view rests partly on the observation that while neither muscle juice alone nor a boiled extract of pancreas alone can destroy sugar *in vitro*, muscle juice to which pancreatic juice is added does destroy sugar.

The formation of this internal secretion is attributed by many observers to the islets of Langerhans, which are scattered throughout the pancreas (fig. 130). The cells forming these islets differ in appearance from the secretory cells of the acini of the pancreas, and contain numerous fine granules which do not stain with eosin, as do the

secretory granules, but can be stained by neutral gentian. Further, the islets do not communicate with the secretory ducts, and are clearly not concerned with the formation of pancreatic juice.

That the islets probably take some part in carbohydrate metabolism is shown by two observations. In the first place, ligature of the pancreatic duct leads, eventually, to atrophy of the secreting tissue, but the islets

FIG. 130.—Islet of Langerhans in pancreas. (From Homans, *Proc. Roy. Soc.*)

are unaffected and glycosuria does not occur. Secondly, it might be expected that, if the islets produce an internal secretion essential for normal carbohydrate metabolism, the removal of the greater part of the pancreas would lead to over-activity of the islets still remaining in the body, which might be demonstrated by histological or other methods; and this has recently been found to be the case. When the pancreas is almost completely removed, only a small fragment being left intact, the animal remains well for a time, but eventually developes diabetes of a

mild character. Subsequent examination of the small pieces of pancreas left in the animal reveals the fact that the islet tissue has lost its granules, and has undergone other histological changes. It has yet to be proved, however, that these changes are the cause and not a result of the diabetes.

The manner in which the internal secretion of the pancreas influences carbohydrate metabolism is still obscure. Recent observations by Starling show that the heart of a diabetic dog still possesses the power of taking up sugar from the blood and utilising it, though probably to a lesser degree than in the normal animal. Moreover, the respiratory quotient in dogs, after extirpation of the pancreas, can be raised by a liberal carbohydrate diet, an observation which suggests that their tissues still possess some power of using carbohydrate. It is possible, therefore, that the lessened capacity of the tissues to oxidise sugar may not be the only factor concerned in experimental pancreatic diabetes.

(6) *Diabetes in man* is a progressive disease characterised by glycosuria, and due to a gradual failure of the tissues to assimilate and oxidise dextrose, as is evidenced by the low respiratory quotient. At first the sugar is derived only from carbohydrate, but eventually it is also formed from protein, which is broken down to a larger extent in order to supply to the tissues energy, which they cannot get from carbohydrate. In the later stages of the disease the urine contains β-oxybutyric acid and its products, often in large amount; and the accumulation of this acid in the body ultimately leads to poisoning of the tissue-cells, which brings about coma and death. The blood contains an excess of sugar, and after death the liver is almost free from glycogen; in most cases the pancreas shows signs of disease, but in others it appears normal. Whether diabetes depends upon the deficiency or absence of an internal secretion from the pancreas is not known, though from analogy with experimental diabetes this seems very probable.

SECTION IV.

PROTEIN METABOLISM.

The products of the digestion of protein are absorbed almost entirely as amino-acids, and there is no direct evidence that they are synthesised into protein in the walls of the villi. On the contrary, there is no doubt that the amino-acids enter the blood stream as such, and their presence in the circulating blood can be demonstrated by the following means.

An artery of an anæsthetised animal is connected with one end of a series of tubes, the walls of which consist of a thin collodion membrane,

the other end being attached to a large vein. The system of tubes is filled with saline solution, and hirudin is injected into the animal to prevent clotting of the blood; the blood is then allowed to flow from the artery through the tubes and back to the vein, a continuous circulation of the animal's blood being thus maintained through the tubes. The tubes are surrounded by normal saline solution at the body temperature, and, as the blood flows through them, its diffusible constituents, including sugar and amino-acids, pass through the collodion wall into the saline solution and can be subsequently examined. Since amino-acids diffuse into the salt solution, they must have been previously present in the circulating blood

Deamination.—Immediately after their absorption amino-acids undergo a change, which is called deamination, and which consists in the removal of the amino-group, and its replacement by an oxygen or hydroxyl radicle. A simple illustration of this change is represented in the following equation:—

$$\underset{\text{Alanine.}}{CH_3 . CH . NH_2 . COOH} + H_2O = \underset{\text{Lactic acid.}}{CH_3 . CHOH . COOH} + NH_3.$$

The amino-acids are thus converted into oxy- or keto-acids, which on reduction become ordinary fatty acids. This change is probably brought about by an enzyme, and takes place partly in the walls of the intestine itself and partly in the liver. Its occurrence in the intestinal wall is shown by the fact that the amount of ammonia present in the portal blood is increased after a protein meal; that it occurs in the liver is proved by the observation that when amino-acids are added to pounded liver substance under aseptic conditions, the amount of ammonia rapidly increases. The extent to which this change in the amino-acids takes place is not known, but a fraction of these acids enters the general circulation without undergoing deamination. The removal of the amino-group does not appreciably diminish the calorie value of amino-acids or their usefulness as a source of energy to the body. Thus the calorie value of 1 gram molecule of alanine is 389; if its amino group is replaced by hydrogen, the calorie value of the propionic acid thus formed is 367, the difference being comparatively trivial.

FORMATION OF UREA.

The ammonia set free by the deamination of amino-acids in the intestinal wall is carried in the portal circulation to the liver, and, together with that similarly formed in the liver itself, is converted into urea. If we regard the ammonia set free as entering into combination

with carbonic acid to form ammonium carbonate, or carbamate, the change taking place in the liver may be represented thus:—

$$(1) \qquad \left.\begin{matrix} NH_4 \\ NH_4 \end{matrix}\right\rangle CO_3 - 2H_2O = CO\left\langle\begin{matrix} NH_2 \\ NH_2 \end{matrix}\right. . \quad \text{Urea.}$$

$$(2) \qquad CO\left\langle\begin{matrix} ONH_4 \\ NH_2 \end{matrix}\right. - H_2O = CO\left\langle\begin{matrix} NH_2 \\ NH_2 \end{matrix}\right. .$$

The formation of urea in the liver has been proved in several ways. In the first place, when the liver of a recently killed animal is removed from the body and perfused with oxygenated blood to which ammonium carbonate or carbamate is added, the ammonium salt gradually disappears from the blood, being replaced by urea; this change does not occur when blood containing ammonium salts is perfused through other organs.

Secondly, it is possible to unite the portal vein with the inferior vena cava in such a way that the blood flowing from the digestive tract along the portal vein is diverted into the vena cava, and thus into the general circulation, without going through the liver; the fistula between the two veins is known as Eck's fistula. The liver is still supplied, in this case, with blood through the hepatic artery. Dogs in which such a fistula has been made remain well when their diet consists chiefly of carbohydrate, but when they are fed on meat or receive ammonium salts or amino-acids by the mouth, they become convulsed; during the convulsions their arterial blood contains four or five times as much ammonia as is present in a normal animal, and the percentage of ammonium salts in the urine rises. It may be concluded that the liver, when supplied only with blood from the hepatic artery, can no longer convert into urea the large amounts of ammonia entering the blood after a protein meal.

Thirdly, in extensive disease of the liver in man the amount of ammonia in the urine is increased, and the amount of urea is correspondingly diminished. It is thus evident that the formation of urea from ammonium salts takes place solely in the liver, probably by the action of a synthetic ferment.

Urea can also be formed in other parts of the body and from other substances than ammonium salts, the most important of these being arginine and uric acid. Arginine occurs in the tissues, and can be broken down by a ferment known as arginase into urea and ornithnin; this ferment is most abundant in the liver and kidneys.

ENDOGENOUS AND EXOGENOUS METABOLISM.

When the composition of the urine excreted in 24 hours by a man taking very little protein food is compared with that of the same person when taking an abundance of protein food, very great differences are observed, and are shown in the following table :—

	Abundant Protein Diet.	Percentage of Total Nitrogen.	Low Protein Diet.	Percentage of Total Nitrogen.
Quantity of urine	1170 c.c.	...	385 c.c.	...
Total nitrogen .	16·8 grams	...	3·6 grams	...
Urea ,, .	14·7 ,,	87·5	2·2 ,,	61·7
Ammonia ,, .	0·49 ,,	3·0	0·42 ,,	11·3
Uric acid ,, .	0·18 ,,	1·1	0·09 ,,	2·5
Creatinine ,, .	0·58 ,,	3·6	0·60 ,,	17·2
Total SO_4 . .	3·64 ,,	...	0·76 ,,	...
Inorganic SO_4 .	3·27 ,,	...	0·46 ,,	...
Ethereal SO_4 .	0·19 ,,	...	0·10 ,,	...

The amount of urea and sulphates in the urine is greatly increased by a protein meal, whereas the creatinine and ammonia are but little affected, this difference being due to the fact that the metabolism of protein in the body is of two kinds, *endogenous* and *exogenous*. The metabolic changes concerned in the production of creatinine and most of the uric acid are known as endogenous metabolism, since these substances are formed by the breaking down of protein in the tissues as part of their ordinary wear and tear, and are unaffected by the amount of protein food eaten, unless this contains creatinine or uric acid. On the contrary, the amount of urea and inorganic sulphates in the urine depends chiefly upon the quantity of protein in the food, the urea being formed from the ammonia set free by the deamination of the amino-acids absorbed into the blood stream during digestion. It thus represents a change taking place in the amino-acids before they reach the muscles and other tissues, and is quite independent of the metabolic changes in the tissues themselves. For this reason, the formation of urea and sulphates is described as exogenous metabolism.

The correctness of this view is proved by the rapidity with which urea is excreted in the urine after a protein meal; the excretion of urea begins to increase within two hours after the meal, and within five hours half the total nitrogen taken in with the food may be excreted as urea. It would be almost impossible for the body to have built up the amino-acids into the living tissues, and to have

broken them down into urea within so short a time. The amount of urea in urine, therefore, serves as an index, not of the total katabolism of protein in the tissues, but of the quantity of protein taken in the food; and the removal of ammonia from amino-acid, and its rapid excretion as urea, furnishes a means by which the body rids itself of nitrogen which is not needed, while retaining the resulting oxy-acids as a source of energy.

Endogenous Metabolism.—Protein, or rather the amino-acids formed during its digestion, serves two purposes in the body.

(1) The greater part of the amino-acids, after being deaminated, is carried to the tissues and oxidised to carbonic acid and water, thereby serving as a source of energy.

(2) A certain proportion of the amino-acids is built up in the tissues into living substance to replace that which is constantly being broken down. The proteins in the tissues of different animals and of different tissues in the same animal vary in composition; and the synthesis in each tissue of its characteristic proteins is made possible by the previous disintegration of the proteins in the food into their ultimate constituents, namely amino-acids. These acids are often spoken of, therefore, as "building stones" which can be put together in varying combinations in the building up of the tissues of the body. For this purpose certain amino-acids, or groupings of such acids, are essential, and cannot be manufactured in the body; among these are tryptophane, tyrosine, and phenylalanine. Substances, such as gelatine, which do not contain these groupings cannot act as tissue builders in the body, and therefore cannot maintain life. Again, zein, which is a protein in maize, contains no tryptophane; and animals fed on this protein, with the addition of starch and fat, rapidly waste, and die after a short time, though life can be prolonged by the addition of tryptophane to this diet.

The groupings essential to life probably include certain combinations of amino-acids in the form of polypeptides. These groupings are not destroyed during pancreatic digestion, and an animal can be kept in good health when fed solely on the products of prolonged pancreatic digestion of protein, with the addition of fat, carbohydrate, salts, and water. When protein is broken down by prolonged boiling with dilute mineral acid, animals fed on the amino-acids thus set free, together with fat, carbohydrates, salts, and water, lose weight and die. Evidently pancreatic digestion leaves intact, and hydrolysis by acid destroys, some polypeptides which the tissues cannot form for themselves, although their nature cannot be determined by chemical analysis of the products formed in the two cases.

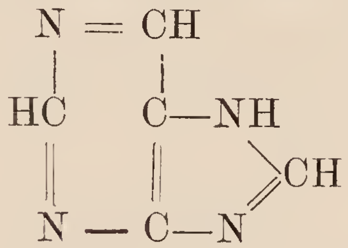
Further, some of the amino-acids seem to be necessary for the production of certain definite substances in the body, one of which perhaps is adrenalin.

Comparatively little is known as to the intermediate stages in the breaking down of protein in the tissues, though the composition of the urine during starvation shows that the end products include urea, uric acid, and creatinine.

PURINE METABOLISM.

The nucleo-proteins of the food are broken down in the digestive tract first into nuclein and protein, the nuclein subsequently undergoing further digestion with the setting free of nucleic acid, which is absorbed unchanged. Nucleic acid, when hydrolysed, is found to consist of the following bodies:—(1) phosphoric acid, (2) purine bases, guanine and adenine, (3) pyrimidine bases, and (4) a carbohydrate which is usually a pentose. The same products are yielded by the disintegration of the nucleins present as nucleo-protein in the tissues. The nucleic acids found in the different tissues vary in composition, and do not necessarily contain all the constituents just mentioned.

The purine bodies are all derivatives of a substance called purine, $C_5H_4N_4$, which has the constitutional formula :—



Purine itself is of purely theoretical interest, but five of its derivatives are found in the body, namely :—

Hypoxanthine (monoxy-purine) . .	$C_5H_4N_4O$.
Xanthine (dioxy-purine)	$C_5H_4N_4O_2$.
Adenine (amino-purine) . . .	$C_5H_3N_4 . NH_2$.
Guanine (amino-oxy-purine) . .	$C_5H_3N_4O . NH_2$.
Uric acid (trioxy-purine)	$C_5H_4N_4O_3$.

After its absorption the nucleic acid taken as nucleo-protein in the food is broken down by a series of enzymes, called *nucleases*, which are found in many tissues, notably the liver and spleen, first into complex groupings called nucleotides, and then into adenine, guanine, and other bodies. Other ferments subsequently convert adenine and guanine by a process of deamination into hypoxanthine and xanthine. Finally, a third set of enzymes oxidise hypoxanthine to xanthine, and

the latter to uric acid. Uric acid is thus the end product of the action of these enzymes on nucleic acid. The whole of the uric acid formed in this way is not excreted as such in the urine, since many tissues, more especially the liver, contain *uricolytic* enzymes, which break down uric acid, one of the products being urea.

The amount of uric acid appearing in the urine does not necessarily represent the whole of that formed from the nucleo-proteins of the food, but is derived partly from them, forming exogenous uric acid, and partly from the breaking down of the nucleins in the tissues, endogenous uric acid. It will be seen from the table on p. 357 that, as a rule, half the uric acid in the urine is of endogenous and half is of exogenous origin.

When the diet is free from nucleo-protein, the excretion of endogenous uric acid is extremely constant, but it is increased after severe muscular exercise and also in fever, owing to a greater breaking down of the nuclei in the cells of the body.

The exogenous fraction varies in amount with the character of the diet, being absent when this contains no nucleo-protein, and increased by food such as kidney, sweetbread, and meat, which are rich either in nucleo-protein or in the precursors of uric acid, such as hypoxanthine.

Nucleo-proteins are not only broken down, but can also be synthesised in the body. In the growing infant, for example, nucleo-protein is rapidly being laid down in the body, although the food (milk) contains hardly any nucleo-protein.

SECTION V.

The separate consideration of the changes undergone by fat, protein, and carbohydrate, though convenient, represents very imperfectly the complex nature of the metabolic changes in the body as a whole. These are greatly influenced both by the nature of the diet and by the absence of one or more of the food-stuffs from the diet.

Starvation.—The metabolism during starvation has been studied in professional fasting men and also in the lower animals. When food is withheld the store of glycogen in the body is rapidly used up, and after two or three days the animal derives its energy solely from fat and protein. The metabolism as a whole is diminished, and the consumption of protein is reduced as far as possible, most of the energy needed by the body being obtained by the oxidation of the fat previously present in the fat depôts. After three or four days the output of nitrogen in the urine reaches a low level, which continues until the body fat has been used up, and the sole source of energy is the tissue protein.

When this stage is reached, the output of nitrogen in the urine shows a sudden rise for a day or two, being followed by a rapid fall in the excretion of nitrogen and by the death of the animal.

The body loses weight, the loss falling most heavily on the less vital organs such as the muscles, whereas the heart and central nervous system lose little or no weight. The breaking down of protein during starvation is probably brought about by a process of *autolysis* or self-digestion in the tissues; the amino-acids formed by the disintegration of the less important tissues are carried in the blood stream and made use of by the vital organs. A similar process of autolysis has been observed in the salmon; during its stay in fresh water the salmon takes no food, and the development of the sexual organs, which takes place during this period, is effected at the expense of the skeletal muscles, which undergo autolysis. In man the character of the metabolism of fat and protein is modified during starvation, as is shown by the appearance of creatine and of β-oxybutyric acid in the urine.

The daily excretion of nitrogen in the urine during starvation amounts in man to 10–12 grams, and it might be expected that if this amount of nitrogen were taken in the form of protein food, it would be used in replacing the daily disintegration of tissue in the body, and would not appear in the urine. Experiment shows, however, that in this case almost the whole of the nitrogen taken in the protein meal appears in the urine in addition to that which was previously being excreted, so that the disintegration of protein is still going on. When protein is the sole article of diet, it is necessary, in fact, to give by the mouth a quantity of protein containing 3 to 5 times as much nitrogen as that which was previously being excreted during starvation in order to obtain a balance between the intake and output of nitrogen. This balance is called *nitrogenous equilibrium.* A further increase in the amount of protein taken by the mouth does not lead to a retention of nitrogen in the body, but the amount of nitrogen excreted increases until nitrogenous equilibrium is again reached at a higher level than before.

Day.	Intake of Nitrogen as Protein.	Output of Nitrogen in Urine.
1	80 grams	80 grams
2	238 ,,	194 ,,
4	238 ,,	220 ,,
6	238 ,,	228 ,,
8	238 ,,	238 ,,

In the experiment recorded in the foregoing table the animal on the first day was in nitrogenous equilibrium. When it received three times as much protein, it again reached nitrogenous equilibrium in the course of the next seven days.

If the food does not consist solely of protein, but also contains fat and carbohydrate, most of the energy of the body is derived from the latter, and nitrogenous equilibrium can be maintained on a comparatively small amount of protein; in this case the protein is used mainly to repair tissue waste.

The Sources of Muscular Energy.—The muscles form about 40 per cent. of the body weight and furnish the greater part of the energy set free as heat or work in the body. This energy is derived from all the food-stuffs, and the fact that the respiratory quotient remains almost unaltered during muscular exercise shows that these food-stuffs must be used nearly in the same proportions during exercise as during rest.

Nature of Diet.	Respiratory Quotient in Man.	
	Rest.	Work.
(1) Rich in carbohydrate . .	0·85	0·90
(2) Poor in carbohydrate . .	0·79	0·82

That being the case, it would be expected that the breaking down of protein in the muscles and the consequent excretion of nitrogen in the urine would be increased by exercise, but observation shows that the amount of nitrogen in the urine is practically unaffected, even by severe exercise. The most probable explanation of this apparent anomaly is that the nitrogenous moiety of muscle protein is resynthesised in the muscle, and therefore does not appear as a waste product.

Although the muscles make use of all the food-stuffs, they derive their energy, both when resting and when active, principally from the food-stuff which is most abundantly supplied to them in the blood. If the diet consists mainly of fat or carbohydrate, these furnish the chief source of muscular energy, and but little energy is derived from protein; when protein is the principal or sole food, it does serve as a source of energy, and the nitrogen in the urine is increased. This has been clearly shown in dogs which were made to do work when fed entirely on lean meat; their bodies contained hardly any fat or carbohydrate, so that protein must have been used as the chief source of muscular energy.

SECTION VI.

THE LIVER.

The liver consists of an enormous number of lobules, each having a diameter of about 1 mm.; they are roughly pear-shaped, and show facets on the surface from mutual compression of adjacent lobules. The stalk of the pear is the point of emergence of a vein, the *intra-lobular* vein, which occupies the centre of a transverse section of the lobule. The substance of the lobule is composed of columns of cells, arranged radially in relation to the intralobular vein. The lobule is surrounded in the pig's liver by a well-marked capsule of connective tissue, containing *interlobular* veins as well as branches of the hepatic artery and the smaller bile ducts. The connective-tissue capsule is continuous with a sheath containing the portal vein, hepatic artery, and bile duct, which enters at the hilum of the liver and is known as Glisson's capsule. This sheath with the contained vessels is called the portal tract. The interlobular veins are branches of the portal vein, and the blood passes from them to the intralobular vein in each lobule through sinusoids, which lie between the columns of liver cells. The sinusoids are wider than capillaries, and their walls are incomplete. The hepatic artery also opens into the sinusoids, supplying oxygenated blood for the nutrition of the liver cells. The intralobular vein opens into a *sublobular* vein, and the sublobular veins unite to form the tributaries of the hepatic vein.

A liver cell is roughly cubical in shape and contains a large spherical nucleus. Its protoplasm is granular, and in the well-fed animal contains accumulations of glycogen, which in the fresh or alcohol-hardened liver can be stained brown with iodine. The cell contains iron in organic combination, which can be demonstrated by treatment with dilute hydrochloric acid and ferrocyanide of potassium; a blue colour is produced. Small droplets of fat may also be present in the cells. Each cell is penetrated by fine canaliculi which are continuous with the bile capillaries, and cavities are also described which communicate with the sinusoids. On the side of each cell which abuts on the adjacent cell is a channel which, with the corresponding channel on the neighbouring cell, forms a bile capillary. The bile capillaries form a network, the contents of which flow into the small bile ducts at the periphery of the lobule. The ducts are lined by cubical epithelium.

Most of the functions of the liver have already been considered in connection with digestion or metabolism, and it is only necessary at this point to summarise these functions.

The liver plays an important part in the metabolism of all three classes of food-stuffs, especially in the preliminary changes which they undergo after absorption. In the first place, it serves as a store-house for glycogen, which it forms from the carbohydrate absorbed during digestion, and which it converts into dextrose and returns to the blood stream in order to keep constant the percentage of sugar in the blood. Secondly, it desaturates the fatty acids reaching it from the fat depôts, and prepares them for the further metabolic changes which occur in the tissues. Thirdly, it removes the amino-group from part of the amino-acids absorbed from the digestive tract, converting them into keto- or oxy-acids and transforming the ammonia thus set free, and also that reaching it from the portal vein, into urea.

Interference with these functions, which sometimes occurs in extensive disease of the liver in man, leads to the appearance of intermediate metabolic products such as leucine, tyrosine, and other substances in the urine, and to disturbance of the normal course of the metabolism of fat; similar effects are seen in animals poisoned with phosphorus, which greatly reduces the metabolic activity of the liver.

The importance of the liver is further shown by the fact that the complete cutting off of its blood supply in mammals is followed by death within a few hours.

In birds, however, the portal system communicates with branches of the renal vein, and so with the systemic venous system; and birds may live for three or four days after the removal of the liver. In these circumstances uric acid, which is the normal end product of nitrogenous metabolism in birds, is largely replaced in the urine by ammonia and lactic acid, which in these animals are the precursors of uric acid.

Apart from its metabolic activities, the other functions of the liver are (1) the secretion of bile, and (2) the conversion of the blood pigment into bile pigment.

CHAPTER XII.

ANIMAL HEAT.

From the point of view of their temperature, animals fall into two groups, namely (1) *poikilothermic*, or cold-blooded animals, whose temperature varies with that of their surroundings, and (2) *homoiothermic*, or warm-blooded animals, whose temperature remains constant except for slight daily variations, and is independent of that of their surroundings.

To the former group belong fishes and amphibia, to the latter birds and mammals, including man. In man the normal temperature is 37° C. (98·4° F.); it shows a daily variation of approximately 1° F., being highest in the afternoon and lowest in the early morning. It is lowered by starvation or prolonged lack of sleep, and is raised by muscular exercise. The constancy of the temperature is due to the fact that heat production and heat loss balance each other.

Production of Heat.—The chemical changes in the body which constitute metabolism involve the production of heat, and this takes place chiefly in the muscles, and to a smaller extent in the liver and other glandular organs; the blood leaving the liver, for instance, is warmer than that entering it. The production of heat in the glandular organs depends mainly on the variations of their activity associated with the digestion of food, and is comparatively constant from day to day. The heat formed in the muscles, however, varies greatly, being enormously increased by muscular exercise; and in warm-blooded animals the amount of heat formed in the body depends largely upon changes in the activity of the skeletal muscles. As has been pointed out (p. 29), the greater part of the energy set free during muscular contraction appears as heat.

The heat formed in the body can be measured by means of a calorimeter, the most suitable form of which for man is the Atwater-Benedict calorimeter (p. 340).

Loss of Heat.—Heat is lost from the body principally through the

skin, and to a smaller extent in warming the expired air and the excreta. On the average, 77 to 80 per cent. of the heat loss takes place through the skin, 17 to 20 per cent. is lost from the lungs, and 3 per cent. in the excreta. The total daily loss varies greatly with the conditions under which the individual is living, being as a rule from 2500 to 3500 calories.

The skin consists of two layers, a superficial layer, the epidermis, consisting of stratified squamous epithelium, and a deeper layer, the dermis, formed of fibrous tissue. The dermis rests upon connective tissue of a looser texture, which is called the subcutaneous tissue and contains a variable amount of fat.

The *epidermis* consists of two principal layers, a deeper layer of cells called the *rete mucosum*, and a superficial layer known as the *stratum corneum* or horny layer. The cells of the rete mucosum are mostly irregular in shape and are connected by protoplasmic bridges, between which are tiny channels along which lymph flows for the nourishment of the cells.

In the horny layer a transformation has occurred whereby the protoplasm has been converted into *keratin*; at the same time the cells have become flattened and scaly and possess no visible nuclei. Between the stratum mucosum and the horny layer can be seen two narrow layers, *stratum granulosum* and *stratum lucidum*, in which the cells are undergoing transformation. The surface cells of the epidermis are continually being shed, and are replaced by the multiplication and subsequent alteration of the cells of the rete mucosum.

The *dermis* consists of dense fibrous tissue which presents papillæ or projections on its surface. The epidermis is moulded on these papillæ, and where they are arranged in rows, as on the palmar surface of the hand and fingers, the epidermis shows corresponding ridges. Blood-vessels run in the dermis and form capillary loops in the papillæ. Lying near the junction of the dermis and subcutaneous tissue over the whole surface of the body are the sweat glands, consisting of coiled tubes, the ducts of which run through the dermis and open into cork-screw-shaped channels in the epidermis leading to the surface.

The skin is protected and kept supple by sebum, which is a fatty material secreted by the sebaceous glands. These glands are found wherever hairs are present, and their ducts open into the upper part of the hair follicles. Each gland is composed of a solid mass of cells, in the central part of which the cells are loaded with fat and the protoplasm has largely disappeared. The fatty material in sebum is not a true fat, but consists chiefly of fatty acids combined with cholesterol.

The secretion of sebum is always taking place, the semi-liquid

central part of the gland being squeezed on to the surface of the skin whenever the hairs are erected by the contraction of the arrector pili muscles. The latter are composed of unstriated muscular fibres, and are attached to the hair follicle and to the epidermis. The sebaceous gland lies between the muscle and the hair follicle.

The Sweat.—Sweat is a clear, colourless fluid containing 99 per cent. of water; sodium chloride is the most abundant solid constituent, and traces of proteins and of urea may also be present.

The secretion of sweat is under the control of the central nervous system, the nerves to the sweat glands belonging entirely to the sympathetic system. Leaving the spinal cord by the anterior roots, they pass to the ganglia of the lateral sympathetic chain, where they have their cell station; from these ganglia non-medullated fibres enter the grey rami, and run with the spinal nerves to their peripheral distribution. Sweating is usually brought about by a rise in the body temperature, and it generally begins as soon as the temperature of the body rises from $\frac{1}{2}$ to 1° C. above the normal. In this case the effective stimulus is the raised temperature of the blood passing through the brain; and sweating may be produced by warming the blood passing through the carotid artery to the brain, even though the temperature of the rest of the body remains unchanged.

Sweating may also be produced reflexly by the local application of heat to the skin, so that one arm, if warmed, may sweat, and not the rest of the body. It is not necessarily associated with increased vascularity of the skin, and may occur, when the sympathetic fibres are stimulated, even in an amputated and therefore bloodless limb.

Hence the skin not only protects the delicate underlying structures and serves as a sense organ, but by means of the secretion of sweat plays an important part in effecting the loss of heat from the body. The loss of heat from the skin is brought about by radiation, convection, and evaporation. Heat passes by convection to the air, or to articles of clothing in contact with the body; it is also lost from the exposed surfaces of the body by radiation to objects at a distance. The loss thus taking place is greater when the blood-vessels of the skin are dilated and the skin is flushed than when the vessels are constricted.

More important than either of these is the loss of heat by the evaporation of sweat, which is continually being formed on the surface of the skin. When the amount of sweat is small it evaporates so quickly as to be unnoticed, the process being called *insensible perspiration.* When the amount formed is increased, or its immediate evaporation is prevented, it becomes visible on the surface of the skin as *sensible perspiration.*

In the process of evaporation much heat becomes latent and is lost to the body; and the rate at which this loss takes place may be increased either by greater formation of sweat or by hastening the rate of evaporation by exposing the body to a current of air.

Conversely the loss of heat in this way is checked when an individual is surrounded by air which is already nearly saturated with moisture. Owing to the heat taken up by water as it evaporates, heat continues to be lost even when the temperature of the surrounding air is higher than that of the body, provided the air is dry; and in tropical climates the loss of heat from the skin takes place chiefly by evaporation.

When sweating is very profuse, the amount of heat lost by the skin relatively to that lost through the lungs is increased, whereas, when the skin is cold and perspiration is scanty, the reverse is the case. In dogs, in which, owing to their hairy coat and paucity of sweat glands, loss of heat by evaporation is comparatively slight, an increase in the loss of heat is largely effected by increased respiratory movements.

The Regulation of Temperature.—In cold-blooded animals the amount of carbonic acid given off from the body varies directly with the temperature of their surroundings; and their metabolic activities, including the production of heat, rise with the temperature, resembling in this respect chemical reactions in the laboratory, which are accelerated at a higher temperature. These animals possess no regulative nervous mechanism by which they can counteract the effects of heat or cold. When the surrounding temperature falls, their metabolic activities diminish until they sink into a state of torpor. When the temperature rises, their metabolic activities increase, and their only means of evading the ill effects of an unduly high temperature is to hide in a stream or to burrow into moist earth.

The maintenance of a constant temperature in warm-blooded animals is effected by an exact adjustment through the central nervous system of the heat production and heat loss. That the production of heat takes place mainly in the muscles and is under the control of the central nervous system is shown by two observations. In the first place, when the motor nerve endings are paralysed by curare so that the muscles are cut off from nervous influences, the animal behaves like a cold-blooded animal. Secondly, when the spinal cord is injured in man or in the lower animals in such a way that the lower part of the body no longer receives impulses from the brain, this portion becomes poikilothermic. When it is warmed, its metabolism becomes more active, and the heat produced warms the blood passing through it, and may be sufficient to raise the temperature of the whole body

several degrees. When it is cooled, its metabolism is diminished, and the temperature of the body may be lowered in spite of the fact that the rest of the body still possesses its regulative mechanism.

The loss of heat from the body depends upon the amount of blood passing through the vessels of the skin and upon the amount of sweat formed, both of these being under the control of the central nervous system. The maintenance of the body temperature when the surrounding air becomes colder might be effected either by an increased production of heat or by a diminished loss of heat. In many animals the adaptation is brought about by changes in the production of heat, more heat being evolved; in man the adjustment is made in a more economical manner chiefly by variations in the heat loss, and to a much smaller extent by alterations in the production of heat. On a cold day the vessels of the skin are constricted, so as to diminish the loss of heat by radiation and convection, and the formation of sweat is scanty. Conversely, on a hot day the skin is flushed and moist, and the loss of heat is more marked.

Within moderate limits of external temperature the production of heat varies but little, though it is diminished when the surrounding temperature becomes high. During muscular exercise both heat production and heat loss are increased, the production exceeding the loss, so that for a time the temperature rises above the normal level.

The intimate relation between heat production and heat loss is also shown in the relationship between production of heat and the size of the animal. The greater loss of heat relative to its weight which occurs in a small animal is met by a correspondingly larger production of heat, with the result that the animal's temperature remains constant. In many animals, including man, the regulative mechanism is not fully developed at birth; and the temperature of the new-born infant falls unless an excessive loss of heat is prevented by keeping the child in a warm atmosphere.

The part of the nervous system which regulates the production and loss of heat and keeps the temperature constant is not known, though possibly it lies in the corpus striatum, injuries to which have been found to cause a marked rise of temperature. Wherever its seat may be, the mechanism is so perfect that in man the temperature remains constant, whether he lives in the tropics or in the arctic regions, though the adjustment fails when the heat or cold is extreme. When a man is exposed to excessive cold, the temperature gradually falls till consciousness is lost and finally death supervenes. When the surrounding temperature is extremely high, and particularly if loss of heat by sweating is interfered with, the temperature of the body rises, pro-

ducing the condition of *heat stroke*. This occurs more readily if the heat production is also increased, for example by muscular exercise, or if the evaporation of sweat is checked by a humid atmosphere; in these circumstances the regulative mechanism may fail even though the surrounding temperature is not very high.

In fever the temperature of the body is raised, the regulative mechanism again bringing about a balance between heat production and heat loss, but at a higher level than in the normal person. Owing to the raised temperature of the body metabolism is more rapid, the breaking down of the tissues is increased, the output of nitrogen in the urine rises, and a loss of weight generally takes place.

CHAPTER XIII.

FOOD AND DIET.

The substances used as food by man and animals contain protein, fat, carbohydrate, salts, and water; and in order to construct a suitable diet for man, it is necessary to know first what amount of these substances in the food best meets the needs of the body, and secondly, the composition of the different food-stuffs.

The mere composition of the food-stuffs, however, is an uncertain guide to their true nutritive value, since this depends upon the ease with which they can be digested and assimilated; it is important, therefore, that the food should be palatable and digestible.

The food is derived either directly or indirectly from vegetable substances which are synthesised by plants from inorganic materials, the energy of the sun's rays being used in the process. The kinetic energy of the sun's rays is thus transformed into the potential energy of the organic food-stuffs, and when these are consumed their potential energy is again converted into kinetic energy as heat and muscular work.

DIET.

From this point of view, the body may be regarded as a machine which converts potential energy into the kinetic energy of muscular work and heat, the daily loss of kinetic energy being replaced by the potential energy of food. The living tissues also undergo a constant wear and tear, the tissue which is broken down being replaced by the building up of fresh tissue from the digested food stuffs. A suitable diet must thus fulfil two functions. On the one hand, it serves as a source of energy, and, on the other, it contains the constituents necessary to replace the breaking down of the tissues.

(1) **Diet as a Source of Energy.**—Calculating work in terms of heat, it is found that the daily loss of energy in man in the form of heat and work is usually about 3000 large calories. It is less in those who lead a sedentary life, and may be increased by severe exercise to

4000–5000 calories or even more. As we have seen (p. 339), the average physiological calorie value of the food-stuffs is as follows:—

1 gram fat	= 9·3	calories
1 „ carbohydrate	= 4·1	„
1 „ protein	= 4·1	„

From these data it is easy to draw up a diet containing the food-stuffs in such amount that, when oxidised in the body, they will furnish sufficient energy to replace the daily loss. Such diets have been constructed as the result of observations on individuals living in institutions under similar conditions of work and surroundings. The following represents the proportions of the different alimentary principles which have been found most suitable:—

Protein	120 grams	= 492	calories
Fat	60 „	= 558	„
Carbohydrate	500 „	= 2050	„
		3100	

The calorie value of this diet is 3100, but a deduction of at least 5 per cent. must be made for food which, though taken by the mouth, is not absorbed from the digestive tract, being lost to the body in the excreta. The same calorie value could be obtained by combinations of these three food-stuffs in other proportions, and, regarded merely as a source of energy, it seems to be a matter of indifference in what form the calorie value is supplied to the body.

(2) **The Replacement of Wear and Tear.**—In order to replace the breaking down of the tissue proteins, the diet must contain a certain minimum of protein, and much discussion has arisen as to the amount of protein in the food which is most suitable for the needs of the body. Chittenden has put forward the view that the amount of protein consumed by most people is excessive. He considers that it can be largely replaced by fat and carbohydrate as a source of energy, and that a comparatively small amount of protein is needed to repair tissue waste and to maintain nitrogenous equilibrium. Any excess of protein beyond this minimum is regarded by him merely as throwing additional work on the liver and kidneys in excreting its nitrogen. Chittenden found by observation on himself and others that it was possible to maintain health and nitrogenous equilibrium for six to eighteen months, and to carry out muscular work, on a diet containing much less protein than that in the dietary mentioned above; in many cases the daily intake of protein did not exceed 40 to 60 grams.

His views have not met with general acceptance. In the first place, individuals living on such a low protein diet often suffer in general health, and in their ability to resist infection. Secondly, the diet of the infant contains much more protein than the minimum which would be necessary according to Chittenden's view, and, since nature provides more than the minimum of protein, the minimum is probably not the optimum. Thirdly, the protein taken in the food does not merely replace tissue waste, but supplies certain complex chemical groupings which the body cannot make for itself; and it may be necessary that, in order to obtain a sufficient amount of these groups, the body should be supplied with a quantity of protein considerably in excess of the minimum required to replace tissue waste. Such a grouping, for instance, might be tryptophane. Although Chittenden's work has been of value in showing that many people eat too much protein, yet the actual amount needed by the body is probably much higher than that taken in his experiments; and we may regard 110 to 120 grams of protein daily as representing the optimum intake for most men. The protein requirements of women are rather less, being from 90 to 100 grams. Under conditions of severe muscular stress, for example in soldiers during war time, considerably larger amounts of protein may be necessary to maintain health.

Although the diet in man usually conforms in a general way to the principles just laid down, it must be remembered that wide individual variations occur and are compatible with health; and it is impossible to formulate any arbitrary laws as to diet.

In addition to serving as a source of energy and to supplying a sufficiency of protein, the food normally contains certain substances, essential to health and even to life, which have been called *vitamines*. Their existence was first shown in connection with the disease known as beri-beri, which is characterised by nervous symptoms and by wasting; it occurs in individuals whose diet consists solely, or almost solely, of "polished" rice, that is rice from which the husk has been removed. A similar condition is produced in fowls, when placed on this diet, and can be cured by the addition to the diet of a substance extracted from the husk of rice; this substance is not a protein, but is probably a basic nitrogenous body, and very small amounts of it are sufficient to relieve the symptoms in birds. In man, beri-beri is cured or prevented by a diet of unpolished rice, or by the addition of yeast, meat juice, or other substances to the food.

It is probable, though not proved, that other diseases, such as scurvy, are also brought about by the absence from the food of vitamines which are present in fresh milk, lemon juice, and meat juice.

The vitamines in milk are destroyed by prolonged boiling, and the condition of scurvy rickets, which occurs in infants, may be due to their being fed on a diet devoid of, or deficient in, vitamines.

Diseases which are brought about by the absence from the diet of some essential constituent are called "deficiency diseases"; they do not occur when the diet is sufficiently varied and contains fresh, uncooked food.

The presence in the food of small traces of certain substances seems also to be necessary for growth in young animals. It has been found that when young rats are fed upon an artificial milk containing perfectly pure caseinogen, fat, and milk sugar in the same proportions as in milk, together with salts and water, the animals fail to grow, although their diet is adequate both as a source of energy and as regards the amount of protein present. On the addition to the diet of very small quantities of fresh milk, growth takes place in a normal manner. Evidently the natural food contains something essential to growth, which is removed in the purification of the constituents of the artificial milk; the nature and mode of action of these substances is quite unknown.

We see, therefore, that in order to maintain health the diet must fulfil the following conditions. In the first place, it must provide sufficient potential energy to replace that lost as work and heat. Secondly, it must contain sufficient protein to replace the breaking down of the tissues, and to provide the complex chemical groupings which the body cannot make for itself. Thirdly, it must contain the substances known as vitamines.

Salts and water also must be present in the diet, although they do not supply energy. Further, in young growing animals the diet, especially protein food, must be relatively more abundant than in adults. Not only is metabolism more active in young animals, but an additional amount of protein is required to provide material for the laying down of new tissue during growth.

THE COMPOSITION OF FOOD-STUFFS.

MILK.

Milk contains all the alimentary principles of a dietary, combined in the proportions necessary for the early stages of life. The proportions of the constituents of milk vary somewhat with the species, as will be seen in the following table :—

	Woman.	Ass.	Cow.
Proteins . .	1·5	1·9	3·5
Fats . . .	3·5	1·4	4·0
Lactose . .	6·5	6·3	4·5
Salts . . .	0·2	0·4	0·7
Water . . .	88·3	90·0	87·3

By a comparison of these figures, it will be seen that cow's milk contains too large a proportion of protein and fat, and too small a proportion of lactose, for the human infant. It is therefore necessary, if an infant is fed on cow's milk, to dilute the latter with water and to add lactose in order to obtain the correct proportions.

Fresh milk has a specific gravity of 1028 to 1034, and is neutral to litmus. Microscopically, it consists of small fat globules floating in an almost colourless fluid, that is, it is a permanent fine emulsion. The globules appear to be prevented from running together by the proteins of the milk forming a fine pellicle on the surface of each globule.

The proteins of milk are caseinogen and lactalbumin. Caseinogen is a phosphoprotein, and is insoluble in water, but soluble in dilute alkalies. It exists in milk as a compound with calcium, and is precipitated by the addition of acetic acid, the precipitate being soluble in excess of the acid. The precipitate of caseinogen obtained from milk by the addition of acetic acid carries down the fats entangled with it, and may be purified from these by washing with ether. When purified, it is a white powder. Lactalbumin remains in the filtrate when the caseinogen and fats have been filtered off. If the excess of acid in the filtrate be almost neutralised so that only a trace of acidity remains, the lactalbumin may be coagulated by heating the fluid.

The fats of milk consist mainly of tripalmitin, tristearin, and triolein. There are, in addition, small quantities of fatty acids lower in the scale—myristic, caproic, caprylic, capric, and lauric. Lactose is the carbohydrate present in milk. It is a disaccharide, $C_{12}H_{22}O_{11}$, and reduces an alkaline solution of copper sulphate on boiling. It is not fermented by ordinary yeast, and in this way it can be distinguished from dextrose. It can be obtained from the filtrate from milk, after removal of the proteins and fats, by slow evaporation, when it crystallises out. The enzyme lactase, by which lactose is converted during digestion into dextrose and galactose, is especially abundant in young animals.

The salts of milk consist chiefly of phosphates and chlorides of potassium, sodium, calcium, magnesium, and iron, calcium phosphate

being most abundant. Analyses have shown that these salts are present in the milk of any one species in exactly the same proportions in which they occur in the young animal which is nourished on that milk. The large proportion of calcium phosphate is of especial importance in view of the formation of bone in the growing animal.

When milk is allowed to stand it becomes sour. The acidity is due to the formation of lactic acid from the lactose by the agency of certain organisms, such as *bacterium lactis*, present in the milk. The growth of these germs is facilitated by warmth. The lactic acid has the same effect on the caseinogen as the addition of acetic acid; that is, it precipitates the caseinogen, and the latter entangles the fats, forming a curd. The precipitation of caseinogen in this way must not be confused with the clotting of milk which is brought about by ferment action in the stomach (p. 304). In the latter process the caseinogen undergoes a chemical change, being converted into casein.

The suitability of the maternal milk for the needs of the growing animal does not depend only on the fact that the various constituents are in the correct proportions. As has already been pointed out, every protein consists of a characteristic grouping of amino-acids, some of these acids being present to a special extent in one protein, and others in another. Caseinogen is remarkable in that all the amino-acids which enter into the composition of the various proteins are represented in its structure to a greater or less extent, so that it may form a source from which any of the body proteins may be built up. Only glycine is absent from the caseinogen molecule, and glycine can be formed in the body by hydrolysis of the higher acids.

The caseinogen of human milk does not form a firm clot with the "rennet" ferment as does that of cow's milk, but is thrown down in the form of a flocculent precipitate. For this reason cow's milk, even when diluted, does not form a satisfactory substitute for maternal milk in the case of the human infant. Other drawbacks to the "bottle-feeding" of infants are (1) the difficulty of obtaining sterile cow's milk; (2) the fact that sterilisation can only be effected at the cost of losing a proportion of the vitamines; and (3) the loss to the child of anti-bodies, which are present in the maternal milk, and help to protect it from certain infective diseases.

Food-stuffs derived from Milk.—The *cream* of milk contains 14 to 44 per cent. of fats, and is a useful form of administering fat when an extra amount is required in the dietary.

Butter is obtained by separating the fats from cream, and is almost pure fat with a small percentage of water.

Cheese is made by the compression of clotted milk so as to express

as much as possible of the water. Cheese is thus rich in protein and fat, the protein being chiefly casein.

BREAD.

Flour contains 68 per cent. of starch, 12 per cent. of proteins, and small quantities of cellulose, fats, and salts. When it is kneaded with water, a change takes place in its proteins. These are two in number: *gliadin*, which is soluble in alcohol, and *glutelin*, which is insoluble in alcohol. When flour is mixed with water these two substances are converted into the sticky material, *gluten*. Dough is thus formed mainly of gluten and starch. It is made spongy by the liberation of gases in its interior, usually by the action of yeast. In the process of baking, the starch in that portion of the loaf which is most exposed to the high temperature, namely, the crust, is partially converted into dextrin and dextrose.

BEEF.

The composition of lean beef is given in the table on p. 378. Fat beef contains nearly as much protein, more fat, and less water. Mutton, poultry, and white fish contain about the same proportions of the various constituents, but poultry contains rather more protein and a smaller proportion of salts, whereas white fish contains less salt and more water.

EGGS.

The white of egg contains three proteins, egg-albumin, egg-globulin, and ovomucoid. The yolk contains a small amount of a phospho-protein, vitellin, and a large proportion of fats, with smaller quantities of cholesterol, lecithin, sugar, and salts.

GREEN VEGETABLES.

Green vegetables are of little value as a source of proteins, carbohydrates, and fats. They have, however, three important functions in a dietary: (1) as a source of iron, (2) as a source of vitamines, the absence of which leads to the onset of scurvy, and (3) as stimulants to the peristaltic movements of the digestive tract, in virtue of the indigestible cellulose which they contain.

GELATIN.

Gelatin is a sclero-protein, and is formed by boiling collagen, the principal solid constituent of connective tissue. Gelatin cannot replace other proteins in a dietary, because it is deficient in three essential amino-acid groups, phenylalanine, tyrosine, and tryptophane. Tyrosine is oxy-phenylamino-propionic acid, tryptophane is indolamino-propionic acid;

and these substances are essential for the building up of the body proteins. In one experiment on a dog, it was found that nitrogenous equilibrium could be maintained when five-sixths of the protein of the diet was replaced by gelatin. In other experiments on animals, it has been found possible to maintain nitrogenous equilibrium for a time on a diet of gelatin to which tyrosine and tryptophane were added. But gelatin alone cannot supply all the amino-acids necessary for the maintenance of animal life.

BEVERAGES.

Tea and *coffee* owe their fragrance to aromatic substances and their stimulating properties to the presence of caffeine or trimethyldioxypurine. *Cocoa* contains about 30 per cent. of fat and 20 per cent. of protein, and is therefore a food. It has also stimulating properties owing to the presence of theobromine, or dimethyldioxypurine. The methylpurines contained in these beverages do not give rise to uric acid in the body, but are excreted unchanged.

Alcohol undergoes oxidation in the body to a limited extent, and to that extent it acts as a food. Its value as a food is, however, counterbalanced by its action as a poison. If taken in any quantity, it interferes first with the higher mechanism for inhibition, later it disturbs the mechanism for muscular co-ordination, and finally it paralyses the whole nervous system. The continued use of alcohol, moreover, leads to degenerative changes in the tissues and organs of the body, and in that way it shortens life.

THE CONSTRUCTION OF A DIETARY.

The amount of protein, carbohydrate, fat, salts, and water required daily being known, a dietary can be constructed with the aid of a table showing the composition of food-stuffs, such as that given below.

Approximate Composition of some Common Food-stuffs.

	Protein.	Carbo-hydrate.	Fat.	Salts.	Water.	Cellulose.
Lean beef . .	21·0	...	1·5	1·0	76·5	...
Eggs . . .	14·8	...	10·5	1·0	73·7	...
Milk (cow) . .	3 5	4·5	4·0	0·7	87·3	...
Cheese . .	33·0	...	27·0	4·0	36·0	...
Peas (dried) .	21·0	55·4	0·5	2·6	13·0	7·5
Oatmeal . .	14·6	65·1	10·1	2·1	5·0	3·1
Bread . . .	6·5	51·2	1·0	1·0	40·0	0·3
Potatoes . .	2·2	18·0	0·1	1·0	78·3	0·4
Carrots . .	0·5	10·1	0·5	0·9	86·5	1·5
Butter . .	1·0	1·0	82·0	1·0	15·0	...

It will be observed that the animal foods are especially rich in protein and fat, and in ordinary life most of the necessary protein is taken in the form of beef, mutton, and eggs. Vegetable foods, on the other hand, are the chief source of carbohydrates, and the latter substances in a dietary are usually derived from bread, rice, and potatoes. Some vegetable foods contain a considerable amount of protein, but the vegetable proteins are not so easily and completely digested and assimilated as those contained in animal food, and therefore from a physiological point of view it is more wasteful to obtain the necessary protein from vegetable than from animal sources. Moreover, in order to get the requisite amount of protein, a vegetable diet must be considerably more bulky than a diet which is partly composed of animal substances.

If the amounts of the alimentary principles required daily be taken as:

Protein	120 grams
Carbohydrate . . .	500 ,,
Fat	60 ,,
Salts	30 ,,

a dietary may be constructed from the table of food-stuffs as follows :—

	Protein.	Carbohydrate.	Fat.	Salts.
500 grams bread . . .	31·5	256	7·5	5·0
220 ,, lean meat . .	46·0	...	3·3	2·2
600 ,, milk . . .	21·0	27	24·0	4·2
20 ,, butter . . .	...	..	18·0	0·2
100 ,, rice . . .	...	76	...	...
400 ,, potatoes . . .	8·8	72	0·4	4·0
100 ,, oatmeal . . .	14·6	65	10·0	2·0
	121·9	496	63·2	17·6
Calorie value	3121			

Rice, which is included in this dietary, contains 76 per cent. of starch and minute quantities of fat and protein. It will be observed that the salt content of the diet is deficient, and would have to be supplemented by means of common salt.

CHAPTER XIV.

THE URINARY SYSTEM.

SECTION I.

THE STRUCTURE OF THE KIDNEY.

The kidney is a compound tubular gland having a duct, the ureter, which connects it with the bladder and is expanded at its upper end to form the pelvis of the kidney. On dividing the kidney lengthwise from its outer to its inner border, it is seen to consist of two layers, an outer reddish-brown cortex, and an inner pale layer, the medulla. The latter is composed of a number of pyramids, the apices of which project as papillæ into the pelvis of the kidney. The larger subdivisions of the renal artery and vein lie between the cortex and medulla, this region being known as the boundary zone. Prolongations of the medullary tissue extend radially into the cortex, forming the medullary rays.

The kidney consists of a mass of tubules, held together by connective tissue. Each tubule begins in the cortex by a blind expanded end (Bowman's capsule), which may be compared with a small ball indented so that its opposing walls almost touch; these walls consist of a single layer of flattened epithelium. A bunch of capillaries, known as a *glomerulus*, projects into the indentation, and together with Bowman's capsule forms a Malpighian body. At the pole opposite the entrance of the blood-vessels Bowman's capsule opens into the tubule proper, which at first takes a tortuous course and is known as the first convoluted tubule; it then becomes spiral or nearly straight (spiral tubule), and passes into the medulla, where it forms a loop (loop of Henle) and returns into the cortex. Here it becomes irregularly zigzag (zigzag tubule), and then convoluted (second convoluted tubule), and ultimately joins a straight collecting tubule (fig. 131). The collecting tubules run into the medulla, and open at the apices of the pyramids into the pelvis of the kidney.

The convoluted, spiral, and zigzag tubules are lined by columnar or cubical cells, the lateral surfaces of which dovetail into each other; they are very granular, the granules tending to be arranged in rows at right angles to the lumen, so that the cells have a rodded appearance. The descending part of the loop of Henle is lined by clear, flattened

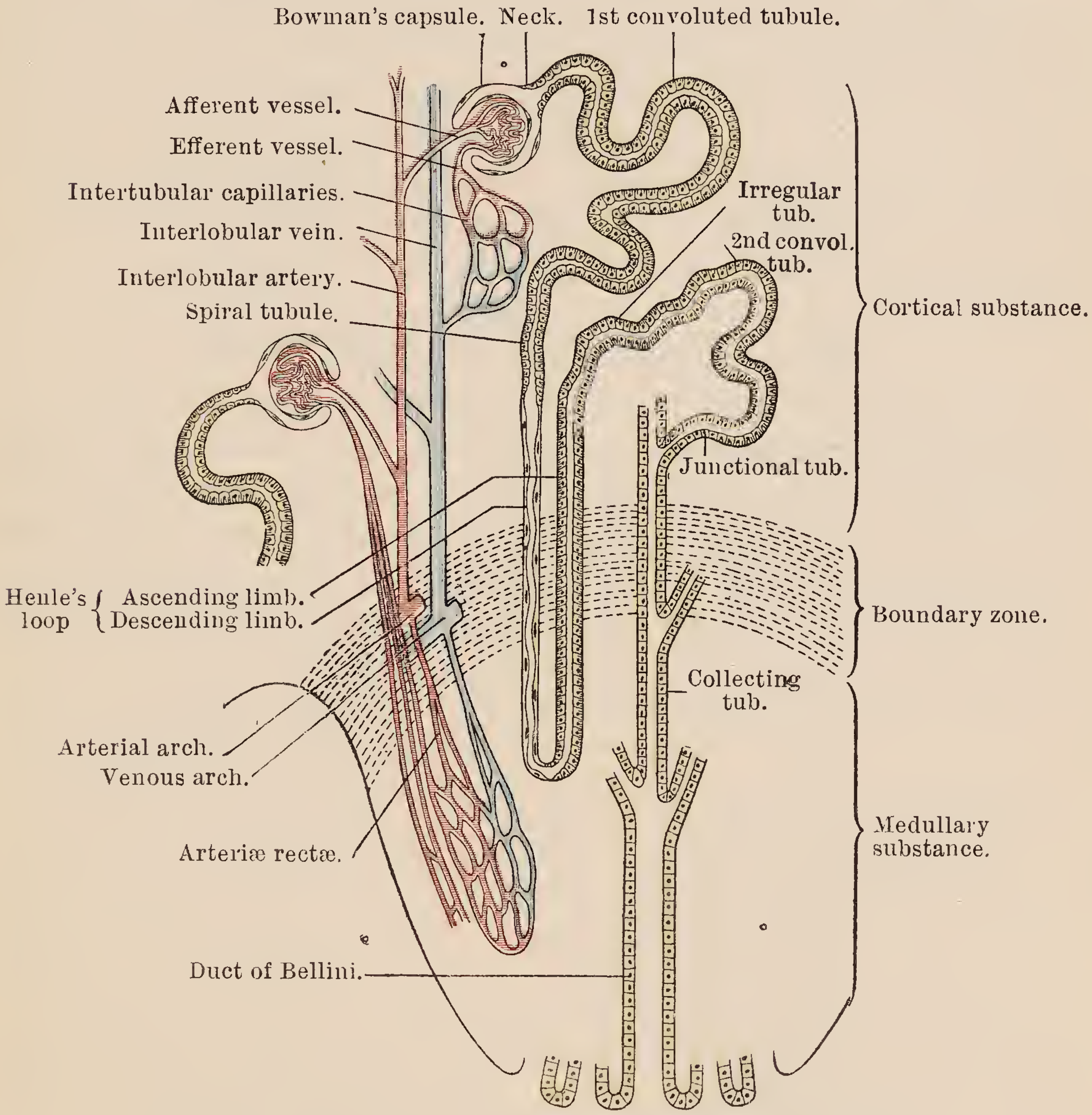


FIG. 131.—Scheme of renal tubule and its vascular supply. (From Gray's *Anatomy*.)

epithelium; the cells of the ascending limb resemble those of the convoluted tubules. The collecting tubules are lined by clear, cubical cells. Throughout the whole length of the tubules the cells rest upon a well-marked basement membrane. The tubule thus consists of (1) Bowman's capsule, (2) first convoluted and spiral tubule, (3) loop of Henle, (4) zigzag and second convoluted tubule, and (5) collecting tubule.

The Blood Supply.—The renal artery enters the kidney close to the origin of the ureter, and divides into branches, which form incomplete

arches lying in the boundary zone between the cortex and the medulla. From these arches vessels pass outwards in the cortex, and give off short afferent branches, each of which ends in a glomerulus. The blood leaves the capillaries of the glomerulus by an efferent vessel, which is smaller than the afferent, and after a short course breaks up into capillaries round the convoluted tubules; from these capillaries the blood passes into veins running to the boundary zone, and opening into venous arches parallel with the arterial arches. The veins ultimately unite to form the renal vein. Straight branches also arise from the arterial arches to end in capillaries round the tubules in the medulla; from these the blood passes back to the venous arches.

THE COMPOSITION OF THE URINE.

Normal human urine is a clear, yellow fluid, acid in reaction, and containing about 4 per cent. of total solids; it is free from cells and from protein, except for a small trace of nucleo-protein derived from the bladder and urinary passages. Its specific gravity varies from 1015 to 1025, and its daily amount is about 1500 c.c. Its average composition is shown in the following table:—

Total quantity of urine . . .	1500	c.c.
,, solids	60	grams.
,, urea	33	,,
,, uric acid	0·75	,,
,, hippuric acid	0·5	,,
,, sodium chloride . . .	15·0	,,
,, phosphoric acid . . .	2·5	,,
,, sulphuric acid	2·5	,,
,, ammonia	0·75	,,
,, creatinine	1·0	,,
,, potassium . . . . }		
,, calcium . . . . }	4·0	,,
,, magnesium . . . . }		

Since the nitrogenous end-products of the metabolism of protein are excreted almost entirely in the urine, its composition largely depends upon the quantity of protein food consumed, and on the katabolic changes in the tissue proteins. The characters of urine vary, therefore, not only in different individuals, but even in the same individual from day to day, and almost from hour to hour.

Amount and Specific Gravity.—The fluid taken by the mouth leaves the body partly in the urine, and partly through the skin and lungs.

In hot weather or during exercise, when evaporation of sweat from the skin is considerable, the urine is decreased in amount and is proportionally concentrated. When the secretion of sweat is scanty, for example on a cold day, a larger proportion of water is excreted by the kidneys, and the urine is abundant and of low specific gravity: copious draughts of water produce the same effect. In diabetes the presence of sugar may raise the specific gravity to 1040 or more, while in some forms of renal disease the specific gravity is always low (1005 to 1015).

Reaction.—The acid reaction of normal urine is due to acid sodium phosphate (NaH_2PO_4); no free acid is present. The bases and acid radicles mentioned in the foregoing table are combined to form salts, and are derived from the food. Sulphuric and phosphoric acid are formed by the oxidation of the sulphur and phosphorus contained in protein, and when the food contains much protein the amount of these acids is increased in the urine, which becomes strongly acid in reaction. Vegetable foods contain organic salts, such as citrates and tartrates of potassium and sodium, in abundance, and in the body these organic acids are completely oxidised, whereas the bases are excreted in the urine. Hence in herbivorous animals, and in man on a vegetarian diet, the urine is neutral or alkaline, though a starving herbivorous animal which is living on its tissue proteins, and is for the time being carnivorous, excretes an acid urine.

Colour.—The colour of urine is almost entirely due to a pigment, *urochrome*, of uncertain origin, the spectrum of which shows no absorption bands. In addition, urine may contain three other pigments, namely, (1) urobilin, (2) uroerythrin, and (3) hæmatoporphyrin.

Urobilin is formed in the digestive tract from bilirubin by bacterial action, and after absorption into the blood is excreted into the urine chiefly as a colourless chromogen, which can be converted into urobilin by the addition of an acid. Urobilin itself occurs in urine in considerable quantity when the amount of bile pigment formed in the liver is increased by an unusually rapid destruction of red cells in the body, for instance in pernicious anæmia. It shows an absorption band at the junction of the green and blue part of the spectrum, and gives a green fluorescence with zinc chloride and ammonia.

Uroerythrin occurs in combination with deposits of urates, giving them a pink colour, which is changed to green on the addition of an alkali; its composition is unknown.

Hæmatoporphyrin (p. 162) normally occurs in minute traces, but may be present in large amount in sulphonal poisoning.

UREA.

The presence of urea in urine may be shown by evaporating the urine to dryness on a water bath, and extracting the residue with acetone (which dissolves urea). On evaporation of the acetone extract the urea crystallises out.

Urea (CON_2H_4) is a solid, crystallising in colourless rhombic prisms which are easily soluble in water, alcohol, and acetone. When heated, the crystals decompose, giving off ammonia and yielding a body called *biuret*. Urea combines with nitric or oxalic acid, forming characteristic crystals, and is decomposed by nitrous acid with the evolution of carbonic acid and nitrogen, or by alkaline sodium hypobromite, according to the following equation:—

$$CON_2H_4 + 3NaBrO = CO_2 + N_2 + 2H_2O + 3NaBr.$$

The carbonic acid is absorbed by the alkali, and the nitrogen is given off; and by collecting and measuring in a graduated cylinder the amount of nitrogen evolved from 5 c.c. of urine, the percentage of urea can be ascertained. Theoretically, 1 gram of urea yields 371 c.c. of nitrogen at 0° C. and 760 mm. Hg, but actually only 354 c.c. are evolved from 1 gram of urea in urine.

Another and more accurate method of estimating the amount of urea is to treat a known volume of urine with an extract of Soya bean, which converts urea into ammonia; the ammonia formed is passed into a known volume of $\frac{N}{10}$ acid, and the amount of uncombined acid is subsequently estimated.

When urine is exposed to the air the urea soon becomes decomposed by micro-organisms, being converted into ammonium carbonate, and the urine becomes strongly alkaline.

The nitrogen present as urea usually forms about 85 per cent. of the total nitrogen existing in one combination or other in the urine. The total nitrogen in urine is estimated by *Kjeldahl's method* as follows:—

A known volume of urine is boiled with pure sulphuric acid until all its carbon is fully oxidised, the nitrogen being converted into ammonia, which combines with the acid. The solution is then made alkaline with caustic potash and boiled, the ammonia, which distils off, being collected in a known volume of $\frac{N}{10}$ sulphuric acid. The amount of acid neutralised by the ammonia is determined by subsequent titration of the uncombined acid with $\frac{N}{10}$ caustic potash.

Urea is the most abundant nitrogenous constituent of urine, its

amount varying, as seen in the Table on p. 357, with the quantity of protein food consumed; in starvation urea is derived entirely from the breaking down of the tissue proteins.

AMMONIA.

The ammonia normally found in the urine represents the small amount which escapes conversion into urea by the liver, and is but little affected by the amount of protein in the diet. In acidosis the abnormal acids formed in the body combine to a large extent with ammonia in the blood, being excreted as ammonium salts in the urine, and the amount of urea is correspondingly diminished. The amount of nitrogen excreted as ammonia in these circumstances is sometimes 20 per cent. or more of the total urinary nitrogen.

CREATININE AND CREATINE.

Creatinine is an anhydride of creatine, which occurs in muscle, and it may be formed from the latter by boiling it with strong hydrochloric acid. It has the formula

$$\begin{array}{lcr} & NH & \text{—————————}\,| \\ & | & | \\ NH = & C - N(CH_3) \,.\, CH_2 \,.\, & CO, \end{array}$$

and gives a red colour with caustic potash and picric acid (Jaffé's test). When creatine is taken by the mouth, either as a pure substance or in meat, some of it may appear in the urine as creatinine. With this exception, the creatinine in urine is derived solely from the endogenous metabolism of protein; and the amount excreted in the urine by the same person from day to day is remarkably constant, and serves as an accurate index of the extent of endogenous protein metabolism.

The origin of creatinine and its relation to the creatine present in muscle are not fully understood, though creatinine appears in the urine in increased amount in fever, and in other conditions in which rapid wasting of muscular tissue is taking place. Creatine also, though not usually present in the urine of adults, is found during starvation, in diabetes, in acute fevers, and in women during involution of the uterus. It is possible that normally the creatinine in the urine is formed from creatine, and that in the conditions just mentioned an increased amount of creatine is set free by protein decomposition, some of which is converted into creatinine, while a portion is excreted in an unaltered form.

URIC ACID.

Uric acid exists in urine in the form of biurates. On adding strong hydrochloric acid to urine and allowing it to stand for twenty-four hours, uric acid separates out as small pigmented crystals having a

characteristic whetstone or dumb-bell shape. It is almost completely insoluble in water, but dissolves in weak alkalies. It slightly reduces Fehling's solution (p. 387), and will also reduce an alkaline solution of silver nitrate (Schiff's test). A solution of uric acid, when evaporated to dryness with nitric acid at a low temperature, yields a purple colour on the subsequent addition of an alkali (murexide test).

The uric acid is derived partly from the nuclein in food and partly from the breaking down of the tissue nucleins.

In addition to uric acid, small amounts of the purine bases are found in urine.

Hippuric acid is synthesised in the kidney from benzoic acid and glycine, the synthesis being brought about by an enzyme. It is the only urinary constituent which is formed in the kidney itself.

Sulphates.—The sulphates are of two kinds, namely, (1) inorganic, and (2) ethereal. The latter are compounds of sulphuric acid with phenol, indoxyl, or skatoxyl, and potassium. Indol and skatol are formed from tryptophane by bacterial action in the digestive tract; and after absorption into the blood they are converted by oxidation into indoxyl and skatoxyl, combined with sulphuric acid, and excreted by the kidneys. Phenol, also, is a product of protein decomposition.

As a rule the ethereal sulphates form about one-tenth of the total sulphates, but when bacterial changes in the digestive tract become excessive (*e.g.* in constipation), the proportion of ethereal sulphates is increased.

Some sulphur is also excreted in organic combination and is known as "neutral" sulphur.

The sulphur of the urinary sulphates is formed almost entirely by the oxidation of the sulphur contained in protein, and the total amount of sulphates varies therefore with the quantity of protein food ingested.

Urine also contains sodium chloride and phosphates, the latter being of two kinds, namely, (1) alkaline phosphates, of sodium and potassium, and (2) earthy phosphates, of calcium and magnesium.

URINARY DEPOSITS.

On standing, normal urine deposits a cloud of mucus (nucleo-protein) derived from the urinary passages. When the urine is concentrated, biurates of sodium and potassium are often deposited as an amorphous sediment, coloured pink by uroerythrin, and dissolving when warmed. Earthy phosphates are deposited from neutral or alkaline urine; they dissolve on the addition of acetic acid. Crystalline

deposits may also occur in urine, and are usually indicative of abnormal processes taking place either in the body or in the urine itself. The nature of the deposits varies with the reaction of the urine.

In acid urine those most frequently seen are, first, uric acid crystals, which assume the form of whetstones or cylinders, and are usually, though not invariably, pigmented; and, secondly, calcium oxalate, occurring as small colourless octohedra, often called "envelope" crystals from their appearance under the microscope.

Uric acid and oxalate crystals are frequently found together. Other crystalline deposits, occasionally met with in acid urine, are cystine (flat hexagonal colourless plates) and the acid urates of sodium or ammonium, which form spheroidal masses with projecting spikes.

In alkaline urine, the crystals most commonly met with are (1) earthy phosphates, star-shaped in appearance, and (2) ammonio-magnesium phosphate, NH_4MgPO_4. The latter, often called "triple phosphate," is formed when urine becomes alkaline as a result of the bacterial decomposition of urea; the crystals are large and very characteristic, resembling knife-rests or coffin lids.

OTHER ABNORMAL CONSTITUENTS IN URINE.

(1) **Coagulable Protein.**—Except for a trace of nucleo-protein, normal urine contains no protein. In disease of the kidney, serum globulin and albumin escape from the blood into the urine, and are coagulated on boiling the urine (after the addition of a drop or two of dilute acetic acid). Further, when urine containing protein is poured on to the surface of strong nitric acid, a precipitate forms at the junction of the two fluids (Heller's test).

(2) **Sugar.**—The conditions under which sugar occurs in urine have already been dealt with (p. 350). In man the usual cause of glycosuria is diabetes, and the sugar is dextrose Lactose is sometimes found during lactation, even in healthy women. In rare cases the urine contains lævulose or pentose. The amount of dextrose present in the urine in diabetes may vary from mere traces up to 350 to 500 grams daily.

Dextrose reduces alkaline solutions of copper sulphate, yielding cuprous oxide. The solutions generally used in testing for dextrose are (1) Fehling's solution, containing copper sulphate, caustic potash, and Rochelle salt, which keeps the cupric hydrate in solution, or (2) Benedict's solution, which contains copper sulphate, sodium carbonate, and sodium citrate. The latter is more satisfactory, since, unlike Fehling's solution, it is not reduced at all by uric acid or creatinine,

nor does it become self-reducing when kept for some time. Other tests for dextrose are (1) the preparation of the osazone with phenylhydrazine and (2) the fermentation test with yeast, which converts dextrose into carbonic acid and alcohol.

The estimation of sugar may be effected by Benedict's method. The solution used contains copper sulphate, sodium carbonate and citrate, potassium thiocyanate, and potassium ferrocyanide. 25 c.c. of the solution and 3 or 4 grams of anhydrous sodium carbonate are placed in a small flask and boiled. The sugar solution is added from a burette until the blue colour of the reagent disappears; this is the end point. The thiocyanate forms a *white* precipitate with the cuprous hydroxide formed by the reduction of the copper sulphate, and the end point is quite sharp. 25 c.c. of the solution are reduced by 0·05 grams of dextrose.

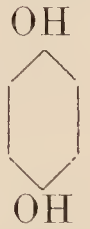
Glycuronic acid ($COOH(CHOH)_4, CHO$) sometimes occurs in urine, either after the administration of certain drugs, such as chloral, or in combination with indoxyl. It reduces Fehling's and Benedict's solutions and forms an osazone, but may be distinguished from dextrose by means of yeast, which does not ferment it.

(3) **Bile** is present in the urine in jaundice, giving it a greenish or brownish colour; its presence may be recognised by Gmelin's or Hay's test (p. 320).

(4) **Blood** occurs in urine as the result of hæmorrhage in the kidneys or urinary passages, and may be identified by observing the red corpuscles under the microscope, or by spectroscopic examination.

(5) **Products of Abnormal Metabolism.**—These include β-oxybutyric acid, diacetic acid and acetone (p. 347), leucine and tyrosine which are present in acute atrophy of the liver, cystine, and homogentisic acid.

Cystine occurs in proteins, and is set free when these break down in the body, but is normally excreted in another form in the urine; in rare cases the cystine derived from protein in the body is excreted as such, and may form crystalline deposits or calculi.

Homogentisic acid,  $CH_2 . COOH$, is a derivative of tyrosine.

In certain persons the oxidation of tyrosine is incomplete, and stops with the production of homogentisic acid, which appears in the urine. The condition is known as *alcaptonuria*, and the urine darkens on standing and reduces Fehling's solution. In persons suffering from alcaptonuria the amount of homogentisic acid in the urine varies from 3 to 6 grams daily; it is proportional to the quantity of phenylalanine and tyrosine present in the proteins of the food, and is increased when these sub-

stances are given as such by the mouth. Thus the whole of the tyrosine and phenylalanine taken into the body is excreted as homogentisic acid. Cystinuria and alcaptonuria, when they occur, are present at birth and persist through life; they are due to "inborn errors" of metabolism, probably to the lack of certain ferments, and do not lead to any disturbance of health.

SECTION II.

THE FORMATION OF URINE.

Broadly speaking, the function of the kidney is to keep the composition of the blood constant by excreting into the urine either abnormal constituents which enter the blood, or any excess of substances normally present, such as water, urea, and sodium chloride. The abolition of this function by the complete removal of the kidneys leads to the retention of the urinary constituents in the blood, and the animal dies in two or three days; the kidneys are, therefore, essential to life. A very important part of their function is to regulate the reaction, that is, the H ion concentration of the blood and tissues. The respiratory mechanism prevents any accumulation of carbonic acid in the blood, while the kidneys control the H ion concentration due to other acids. These organs are extraordinarily sensitive to the slightest change in the reaction of the blood, and respond by excreting in the urine any excess of acid or alkali which is present. Recent observations in man show that in some diseases of the kidneys the normal balance of acid and base in the blood is no longer maintained, and the amount of lactic and other acids in the blood is increased. This increase stimulates the respiratory centre, as already described (p. 268), leading to severe hyperpnœa, and to a fall in the tension of carbonic acid in the blood.

So far as is known, there are no secretory nerves to the kidney; its functional activity is excited solely by any change in the chemical composition and amount of the blood flowing through it, and is thus largely determined by metabolic changes occurring in other parts of the body.

The structure of the renal tubule is extremely complex, much more so than that of most of the other glands of the body; many views have been held as to the function of its different parts, and even now the problem is not completely solved. The structure of the convoluted tubule and of the capsule of Bowman is so different that it seems certain that their functions must also be different; and Bowman, on purely histological grounds, suggested that the glomeruli filtered off

water and salts, the remaining urinary constituents being secreted by the tubules.

Ludwig believed that the whole of the urine was formed by filtration through the glomeruli as a fluid identical in composition with the blood plasma minus its proteins, and that in its passage down the lumen of the tubules much of the water and some of the salts were reabsorbed, so that the composition of urine, as it left the kidney, differed greatly from that of blood plasma. Since blood plasma contains about 0·02 to 0·05 per cent. of urea, whereas urine contains 2 per cent. urea, this theory demands that at least 60 litres of fluid should be filtered off by the glomeruli, of which all but 1·5 litres are reabsorbed; it is no longer accepted.

Heidenhain regarded both the tubules and glomeruli as possessing a secretory function, the latter secreting water and salts by a selective and vital process. This view is still accepted by some authorities, whereas others believe that the glomeruli form by filtration a fluid identical in composition with the blood plasma minus its proteins, and that the tubules secrete into this fluid, as it passes along them, water and other urinary constituents. The latter theory is really a slight modification of Bowman's theory

The question as to whether the formation of urine takes place by a process of filtration or of secretion can be answered by ascertaining whether the conditions under which it is formed conform to those known to hold for filtration or secretion elsewhere. In filtration, the amount of filtrate varies directly with the difference of pressure on the two sides of the filtering membrane, and it usually contains the same percentage of crystalloids as the fluid undergoing filtration. When a true secretion, such as that of saliva, takes place, the pressure of the saliva in the ducts may rise higher than that of the blood, and the amount of secretion is, within wide limits, independent of the blood pressure; moreover, the composition of the secretion differs greatly from that of the blood. Further, during secretion, the secreting cells perform work and take up more oxygen from the blood.

In the discussion of this question it is convenient to consider separately the functions of the glomeruli and of the tubules.

THE FUNCTION OF THE GLOMERULI.

In the mammalian kidney, it is impossible to obtain separately the urine formed by the tubules and glomeruli respectively, though there is evidence that when the flow of urine is profuse it is derived mainly from the glomeruli. If urine is simply filtered through the walls of

the glomeruli, its amount should be increased by raising the capillary pressure in the glomeruli and decreased by lowering that pressure, since the pressure in the ureter is nil, and its composition should be that of blood plasma minus proteins.

Experiment shows that such is the case. The capillary pressure in the kidney is increased by dilatation of its arterioles, so long as the general blood pressure remains constant, or by a rise in the general blood pressure, if this is not accompanied by active constriction of the renal arterioles. In either case the amount of blood flowing through the kidney is increased, and more blood is present in it at any moment. Conversely, the capillary pressure is diminished either by a fall in the general arterial pressure, or by constriction of the arterioles, the general arterial pressure remaining unchanged.

The changes in capillary pressure cannot be observed directly, but may be measured indirectly by recording either the alterations in volume of the kidney, or the rate of blood flow through it by one or other of the methods already described (p. 225); an increase in the volume of the kidney indicates a rise of pressure in the capillaries of the glomeruli.

The capillary pressure in the glomeruli is high, partly because the renal arteries arise directly from the aorta, and partly because the efferent vessels of the glomeruli are smaller than the afferent vessels; it is probably only about 20 to 30 mm. Hg below that in the renal artery.

The kidneys are amply supplied with vaso-constrictor nerves from the sympathetic system, and the calibre of the arterioles can be altered by section or stimulation of these nerves. On section of the renal vaso-constrictor nerves the kidney dilates, the rate of blood flow through it is increased, and more urine is formed; stimulation of the nerves causes shrinking of the kidney, and the flow of urine diminishes or ceases altogether. Division of the spinal cord in the cervical region leads to dilatation of all the arterioles, including those in the kidneys; but the general arterial pressure falls so low that, although the renal arterioles are dilated, the rate of blood flow through the kidney is much diminished and the flow of urine ceases altogether. Stimulation of the spinal cord in the neck leads to constriction of arterioles and a large rise of blood pressure; and the renal arterioles become so constricted that, in spite of the rise in blood pressure, the volume of the kidney is lessened, and the flow of urine is small or absent. The injection of adrenalin has the same effect as stimulation of the spinal cord. These and other experiments make it clear that, as seen in the following table, the amount of urine formed by the kidney varies directly with the volume of the kidney, that is to say,

with the capillary pressure in the glomeruli; and if the arterial blood pressure falls below 40 to 50 mm. Hg, the flow of urine ceases.

Procedure.	General Blood Pressure.	Renal Vessels.	Kidney Volume.	Urinary Flow.
Division of spinal cord in neck	Falls to 40 mm. Hg.	Relaxed.	Shrinks.	Ceases.
Stimulation of cord	Rises.	Constricted.	Shrinks.	Diminished.
Stimulation of cord after section of renal nerves	Rises.	Passively dilated.	Swells.	Increased.
Stimulation of renal nerves	Unaffected.	Constricted.	Shrinks.	Diminished.
Stimulation of splanchnic nerves	Rises.	Constricted.	Shrinks.	Diminished.
Hydræmic plethora	Rises.	Dilated.	Swells.	Increased.
Hæmorrhage	Falls.	Constricted.	Shrinks.	Diminished.

If the blood plasma is filtered through peritoneal membrane soaked in gelatin, it is found that, when the difference of pressure on the two sides of the membrane is 40 mm. Hg or more, the filtrate contains the dissolved constituents of plasma with the exception of protein; with a lower difference of pressure no filtration occurs. This is due to the fact that the proteins in plasma exert an osomotic pressure equal to about 25 mm. Hg, and water tends to pass back by osmosis from the filtrate into the plasma. It is for this reason that the passage of fluid through the glomerular wall ceases when the arterial blood pressure falls below 40 mm. Hg. If the osmotic pressure of the protein is diminished by decreasing the amount of protein in the plasma, for instance by diluting the plasma, urine may be formed when the blood pressure is considerably less than 40 mm. Hg. In hydræmic plethora (p. 240), not only is the plasma more diluted, but the renal vessels are dilated and the pressure in the glomeruli is raised; and the formation of urine may be extremely rapid and profuse.

The difference of pressure on the two sides of the walls of the glomeruli may be diminished either by lowering the capillary pressure or by raising the ureter pressure. When the escape of urine from the ureter is prevented, the formation of urine continues until the pressure in the ureter is 40 to 50 mm. Hg below that in the blood-vessels, after which no more urine is formed.

We may conclude, therefore, that the amount of urine formed by the glomeruli varies directly with the difference of pressure on the two sides of the glomerular membrane, and that it is formed by a purely physical process of filtration. An apparent exception is seen when the renal vein is ligatured: the capillary pressure rises, but the flow of

urine ceases entirely. The reason is that the flow of blood through the glomeruli ceases, and their contents soon consist of little more than a mass of blood corpuscles, rendering filtration impossible.

The more rapidly urine is formed by the kidney, the more nearly does its composition approximate to that of blood plasma; and when the blood is greatly diluted, for example by repeated injections of Ringer's solution, the percentage of sodium chloride and urea in the plasma and the urine may be identical.

ANALYSIS OF PLASMA AND URINE IN HYDRÆMIA. (BARCROFT.)

	Chlorides as NaCl.	Urea.
Plasma . . .	0·88 per cent.	0·04 per cent.
Urine . . .	0·88 ,,	0·05 ,,

Similar results have been obtained in animals, in which the renal tubules were poisoned with corrosive sublimate, or other drugs, so as to eliminate their functions. The fluid formed by the glomeruli appears, therefore, to be isotonic with the blood plasma, a fact which is intelligible if it is formed by filtration, but which does not fall into line with our knowledge of secretion.

FUNCTIONS OF THE TUBULES.

There is no doubt that the renal tubules form urine by a process of secretion, which in its essential features is strictly comparable with that occurring in other secretory glands. In the first place, the composition of the urine formed by the tubules differs greatly from that of the blood. Secondly, increased secretory activity of the tubules is accompanied by a larger consumption of oxygen, and may take place without any alteration in the rate of blood flow through the kidney.

The secretory function of the tubules has been most clearly proved in the frog, in which, owing to the arrangement of the blood supply to the kidneys, the functions of the tubules and glomeruli can be studied separately. The glomeruli are supplied with blood solely through the renal artery, whereas the tubules have a double supply. On the one hand, the efferent vessels from the glomeruli enter the network of vessels round the tubules; on the other hand, the tubules also receive blood from the renal portal vein, which arises from the femoral vein (fig. 132).

When the renal arteries are ligatured in the frog, the circulation

of blood through the glomeruli is completely cut off, but the tubules are still supplied with venous blood from the renal portal vein. The cutting off of the supply of arterial blood to the kidneys is followed by destruction of the epithelium of the tubules, and the frogs secrete no urine. If, however, the frogs are kept in an atmosphere of oxygen after ligature of the renal artery, sufficient oxygen is absorbed and carried to the tubules to replace that normally supplied to them by the arterial blood leaving the glomeruli; and the nutrition of the tubules is maintained. In these circumstances the frogs form small quantities of urine, and, since the glomeruli are excluded, this must come entirely from the renal tubules; it is acid in reaction, and contains urea and salts.

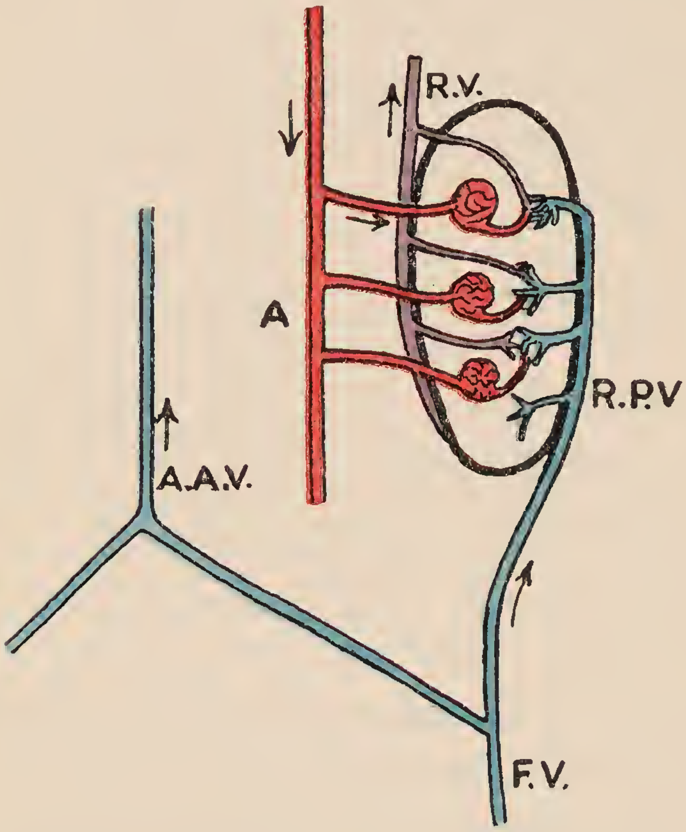


Fig. 132.—The blood supply to the kidney of the frog.

A., aorta; R.V., renal vein; R.P.V., renal-portal vein; F.V., femoral vein; A.A.V., anterior abdominal vein.

In mammals the injection of substances such as sodium sulphate or urea into the blood leads to an increased flow of urine, which then contains a higher percentage of sodium sulphate or urea than is present in the blood; and at the same time the consumption of oxygen by the kidney is greatly increased.

	Oxygen used by Kidney per Gram per Minute.	Percentage of Sodium Sulphate in Urine.
(1) Normal kidney . .	0·04 c.c.	0·26 per cent.
(2) After the injection of sodium sulphate .	0·09 c.c.	1·25 ,,

Since these changes may occur with little or no alteration in the volume of, or the rate of blood flow through, the kidney, the additional urine formed in these experiments must have been secreted by the tubules. This conclusion is confirmed by the fact that when the renal tubules are poisoned with drugs, such as corrosive sublimate, the

injection of sodium sulphate no longer increases the amount of oxygen used by the kidney, and the urine may be isotonic with the blood plasma. This experiment is not quite conclusive in mammals, since the glomeruli, as well as the tubules, are exposed to the poisonous action of corrosive sublimate; and it might be legitimately argued that the glomeruli possess a secretory function, which is abolished in the poisoned kidney. But it is possible in frogs to poison the tubules and to leave the glomeruli intact; and since, when this is done, the urine is isotonic with the fluid passing through the glomeruli, the function of the latter is not secretory, but is that of a filtering membrane.

Further evidence for the secretory function of the tubules is provided by experiments in which indigo-carmine (sulphindigotate of soda), which is a blue pigment, is injected into the blood stream. The spinal cord of the animal is previously divided in the neck, so as to abolish the formation of urine by the glomeruli, and to prevent the dye from being carried away in the urine. The animal is killed ten minutes after the indigo-carmine has been injected, and the kidneys are fixed in absolute alcohol. Sections of the kidneys show the presence of blue granules of the pigment, in the lumen of the tubules, and in the cells of the convoluted tubules, but not in Bowman's capsule or the cells lining it, indicating that the pigment had been secreted by the tubules but not by the glomeruli.

Reaction of Urine.—The fluid filtered off from the glomeruli has the same reaction as the blood plasma, and the acid reaction of normal urine is due to the activity of the cells of the tubules. This can be shown by repeatedly injecting into the dorsal lymph sac of a frog acid fuchsin, which is almost colourless in neutral or alkaline solutions and red in acid solutions. When the kidneys are subsequently examined microscopically, the glomeruli are seen to be colourless, whereas the cells of the convoluted tubules are red.

Further, the more rapidly urine is formed in the mammal, that is, the greater the amount filtered through the glomeruli, the more nearly does its reaction approximate to that of the blood.

It has been thought that the acid reaction of urine is due to the fact that as the glomerular filtrate passes down the tubule an absorption of bases, especially sodium, takes place, so that the urine becomes acid. Since the urine formed by frogs after ligature of the renal arteries is acid in reaction, it is probable that the acid reaction of urine is due to the secretion of acid radicles by the tubules, rather than to the absorption of bases.

In the process of secretion the renal tubules do work which can be approximately measured if the osmotic pressure of the blood plasma

and of the urine are known. The freezing point of any substance in solution in water is lower than that of pure water, and the osmotic pressure of such a solution is proportional to the depression of the freezing point below 0° C. The freezing point of serum is $-0{\cdot}56°$ C., and that of urine may be $-4{\cdot}5°$ C. The osmotic pressure of urine, therefore, is very much greater than that of blood, and the amount of work done by the kidneys in producing urine of high osmotic pressure from blood, of which the osmotic pressure is low, is extremely large.

Absorption by the Tubules.—When a mixture of sodium chloride and sodium sulphate is injected into the circulation of an animal, the percentage of chlorides in the urine gradually falls as the experiment continues, and may become less than that in the blood plasma, while the percentage of sodium sulphate in the urine remains high. This is seen in the following table:—

	Chlorides.	Sulphates.
Blood serum . . .	0·49 per cent.	0·19 per cent.
Urine	0·09 ,,	2·0 ,,

Accepting the view that the glomeruli filter off from the blood a fluid containing the same percentage of sodium chloride as that in the blood, this result can only be explained by supposing that as the glomerular filtrate passes down the tubules they absorb sodium chloride.

Similar results have been obtained in frogs. When the kidneys of the frog are perfused through the renal arteries with oxygenated Ringer's solution, the urine, which in these experiments is formed solely by the glomeruli, is more dilute than the perfusing fluid; this is due to the fact that, as the urine formed by the glomeruli passes down the tubules, the latter absorb sodium chloride. When the tubules are poisoned with corrosive sublimate, absorption no longer takes place, and the urine is isotonic with the perfusing fluid.

This process of absorption probably serves to prevent the loss of salts which are needed in the body, especially when they are not being replaced in the food. That this is the case is suggested by the observation that, when animals are fed for some days on a diet free from chlorides, their urine is almost free from chlorides, although the percentage of sodium chloride in the blood plasma may be unaltered.

In all probability water, and possibly other substances, are also absorbed. The part of the tubule which carries out this process has not been ascertained.

Diuretics.—Substances which, when they enter the blood stream, increase the amount of urine formed by the kidneys are called diuretics. Some act by stimulating the cells of the renal tubules to increased secretory activity; to this group belong urea and sodium sulphate. The ground for believing that they act upon the tubules is that they increase, not only the flow of urine, but also the amount of oxygen consumed by the kidneys.

The diuretics of the other group increase the formation of urine, but do not alter the gaseous exchange of the kidney; they include hypertonic solutions of sodium chloride, potassium nitrate, and other salts. When hypertonic solutions of these salts are injected into the blood, they raise its osmotic pressure and bring about the condition of hydræmic plethora (p. 240). The volume of the kidney and the capillary pressure in the glomeruli are increased; and as a result of this rise of pressure, more fluid is filtered through the walls of the glomeruli. It may be readily shown that diuretics such as sodium chloride have no specific action, but that they increase the flow of urine solely by raising the capillary pressure. If the usual action of these diuretics in raising the capillary pressure is prevented, the injection of the diuretic does not increase the amount of urine; this can be effected by keeping the volume of the kidney constant by means of a screw-clamp placed on the renal artery.

Some diuretics, such as sodium sulphate, produce their effect partly by direct action on the renal tubules by which they are secreted, and partly by producing hydræmic plethora.

Summary.—From the foregoing experiments we may conclude, in the first place, that the glomeruli, in all probability, simply filter off from the blood a fluid identical in composition with blood plasma, excluding protein; the amount of this filtrate normally depends solely upon the capillary pressure in the glomeruli.

Secondly, the tubules secrete into this fluid urea, uric acid, phosphates, sulphates, and other urinary constituents, with some water, the amount of secretion being dependent on the quantity of these substances reaching the kidney in the blood. This will vary with the metabolic activities of the body, with the result that the kidney removes from the blood the waste products constantly entering it from the tissues, and the composition of the blood is kept practically constant.

Thirdly, the tubules possess a selective power of absorption, whereby certain substances such as sodium chloride, which are of importance to the body, can be retained when required. In the normal kidney it is probable that all these processes are taking place simultaneously, one

or other predominating according to circumstances. The drinking of a large quantity of water, for instance, is followed by its rapid excretion through the glomeruli, by which most of the water of the urine is normally excreted.

SECTION III.

MICTURITION.

The urine formed in the kidneys passes along the ureters to the bladder, where it accumulates, the bladder being emptied from time to time by the process of micturition. The flow of urine along the ureters is assisted by rhythmic waves of contraction, passing down from the pelvis of the kidney to the bladder at intervals of a few seconds; they can still be observed in the ureter when it is isolated from the central nervous system.

The wall of the bladder consists of unstriated muscle fibres arranged in three layers, an outer and an inner longitudinal layer, and a middle layer of fibres running circularly; it is lined by transitional epithelium. When the muscular walls contract they lessen the size of the cavity. The escape of urine from the relaxed bladder is prevented by two sphincters, namely, first, circular unstriped muscular fibres, forming a loop round the orifice of the bladder and called the *trigonal sphincter*, and, secondly, the *sphincter urogenitalis*, or compressor urethræ, which encloses the second part of the urethra, and is composed of striated muscular fibres. The bladder receives its nerve supply from (1) the nervi erigentes, stimulation of which causes it to contract, and (2) sympathetic fibres from the hypogastric plexus, stimulation of which is followed in some animals by inhibition and in others by contraction of the bladder wall; afferent fibres also pass from the bladder in the nervi erigentes to the spinal cord.

Micturition is normally carried out as a reflex action which, in the adult, is controlled and can be inhibited by impulses from the higher parts of the brain. Distension of the bladder wall gives rise to impulses which, travelling to the spinal cord, reflexly bring about emptying of the bladder by the contraction of its muscular coat, the nerve cells concerned in the reflex lying in the sacral region of the cord; the escape of urine is made possible by the simultaneous relaxation of the sphincter muscles. The intensity of the afferent impulses varies with the rate of filling of the bladder. When the bladder fills slowly, its muscular wall relaxes, and it may contain a considerable amount of urine before any appreciable tension is placed upon its muscular fibres. On the contrary, when urine is being formed rapidly, the tension within

the bladder may be quickly and greatly increased by the presence of a comparatively small quantity of urine. In man, micturition usually occurs when the pressure within the bladder is about 150 mm. of water; and if the pressure is suddenly raised to this level by injecting fluid through the urethra into the bladder the desire for micturition is experienced.

Transection of the spinal cord in the upper lumbar region does not destroy the reflex mechanism, though it severs the path by which sensory impulses reach the brain and voluntary impulses pass to the sacral centre. By means of voluntary impulses the emptying of the bladder can be inhibited in the adult, but in the infant such impulses are lacking and the act of micturition is purely reflex. The emptying of the bladder is usually assisted by voluntary contraction of the abdominal muscles, and in man such a contraction, by increasing the pressure within the bladder, frequently initiates the reflex action.

When the centre in the sacral region is destroyed, for instance as the result of injury in man, the bladder still reacts like plain muscle elsewhere, and increased tension causes it to contract. As soon as the pressure within the bladder falls below a certain level, however, it fails to overcome the resistance offered by the sphincter muscles, and the bladder is not completely emptied.

CHAPTER XV.

THE DUCTLESS GLANDS.

The ductless glands include a group of organs of very varied functions, the only feature which they have in common being the absence of any secretion passing either to the surface of the body or into the digestive tract. Many of them, however, such as the thyroid, suprarenal, and pituitary glands, do form substances which pass either directly into the blood stream or into the lymph channels and are described as *internal secretions.*

The internal secretions belong to the class of bodies known as hormones, whose general characters have already been dealt with (p. 306), and which are also formed by organs, *e.g.* the pancreas, which possess an external secretion. The presence of these hormones in the body is in many cases essential to health and even to life; and the activity of the internally secreting glands is correlated with and regulates the functions of distant organs, the only link being the blood by which the hormone is carried from its place of origin to its place of action.

Much of our knowledge of the functions of the ductless glands is derived from the study of the symptoms observed in human beings, in whom one or other of them is diseased. Hence it is usual in studying their functions to consider (1) the effects of disease in these glands in man, (2) the effect of their extirpation in animals, and (3) the effects of extracts of the glands, either upon normal animals or as therapeutic agents in man.

THE SUPRARENAL GLANDS.

One suprarenal gland lies at the upper end of each kidney. Each consists of an outer yellowish cortex partially or completely enclosing a darker central portion, the medulla.

The cortex is composed of cells arranged in radial columns and

forming three zones: an outer or *zona glomerulosa*, middle or *zona fasciculata*, and inner or *zona reticularis*. The columns are supported by strands of connective tissue in which lie numerous capillaries; the cells are polyhedral, the cell substance being clear and often containing lipoid globules.

The cells of the medulla are arranged in an irregular network, their protoplasm being granular and often pigmented. The blood supply of the gland is extremely abundant, particularly in the medulla, in which the interstices of the network of cells are occupied by large sinusoids in intimate relation with the medullary cells. The glands are supplied with nerve fibres from the semilunar ganglia, and a few scattered nerve cells are present.

The medullary cells contain a substance which stains brown with chromates, and which, on account of its affinity for chromates, has been described as *chromaffine* material. This is also found, apart from the suprarenal glands, as small masses of tissue (paraganglia) lying along the large abdominal blood-vessels, and in or close to the sympathetic ganglia. The amount of this accessory chromaffine substance varies greatly in different groups of animals.

The cortical and medullary parts of the glands have a different origin, the cortex being developed from mesodermic tissue (the Wolffian body), whereas the medulla is ectodermic, forming part of the primitive sympathetic system, from which it finally becomes separated and differentiated. In some fishes the cortical and medullary tissue persist as anatomically separate organs, and it is not known whether their coalescence into a single organ in mammals implies any physiological relationship between them.

In 1855 Addison pointed out that, in man, a disease of which the chief symptoms are prostration, muscular wasting, vomiting, and pigmentation of the skin, and which ends fatally, is associated with disease or atrophy of the suprarenal glands. This observation was soon followed by the study of the effects of their removal in animals; and it was found that, in mammals, removal of the glands was followed by death in two or three days.

Subsequent investigation has thrown but little light on the functions of the cortical part of the gland, beyond the fact that tumours of the cortex are sometimes associated with abnormally precocious sexual development. In fishes the removal of the interrenal body, which corresponds in structure and origin with the cortex of the mammalian suprarenal gland, is said by some observers to cause death, though others deny this.

The medulla contains a substance, *adrenalin*, which can be ex-

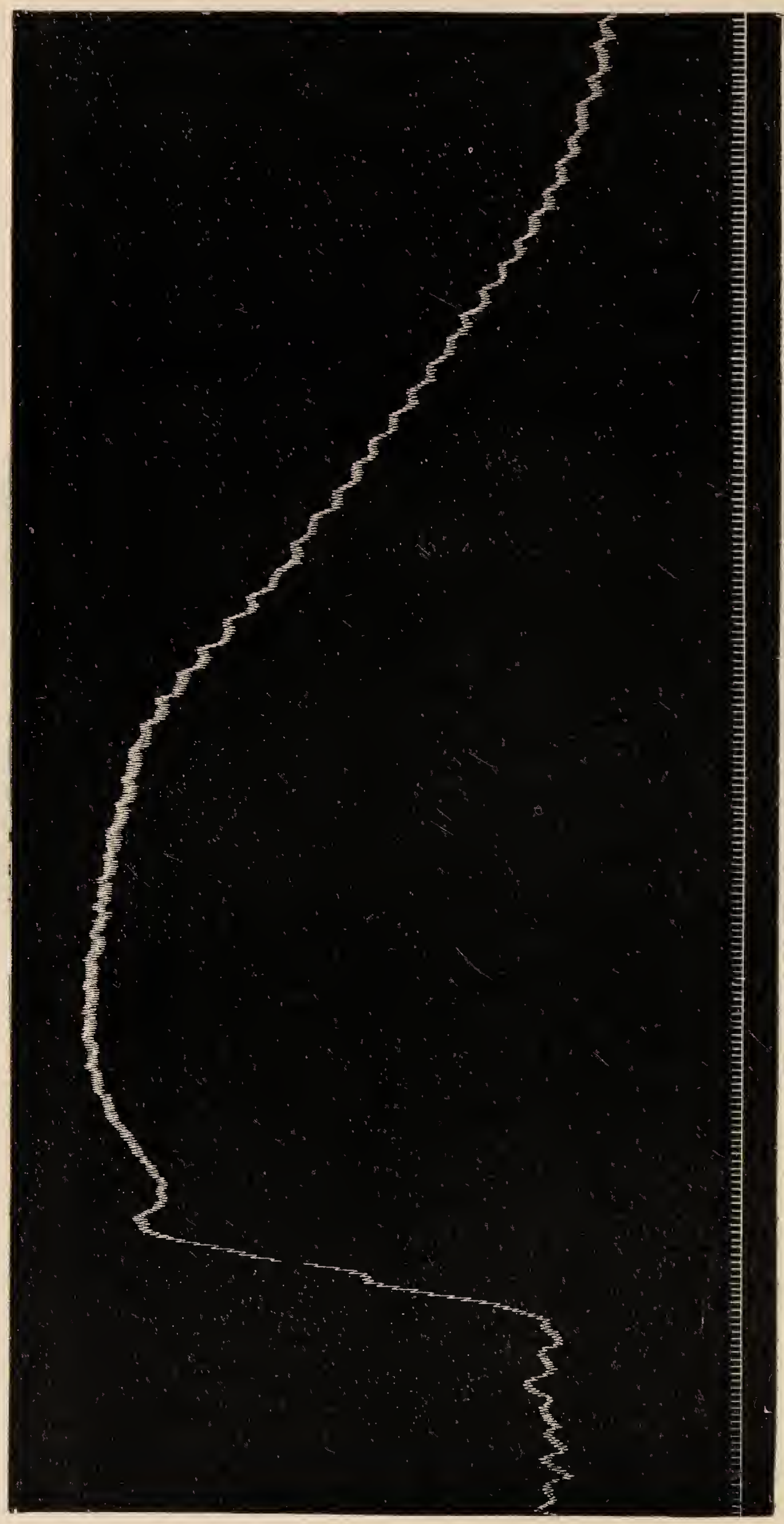
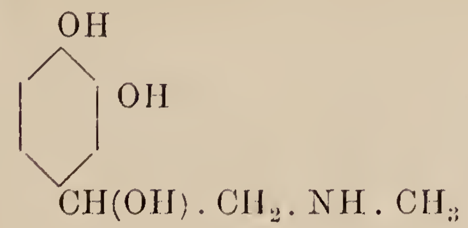


Fig. 133.—Arterial blood pressure. Effect of injection of suprarenal extract. The vagus nerves have been divided. Time in seconds. (From *Practical Physiology*, by Pembrey and others.)

tracted from it in the pure condition, and which has the constitutional formula



Adrenalin has also been prepared synthetically.

The brown staining of the medulla when the gland is hardened in a chromate solution is due to the combination of the chromate with adrenalin, and the depth of the colour is roughly proportional to the amount of adrenalin present. The accessory chromaffine material, which

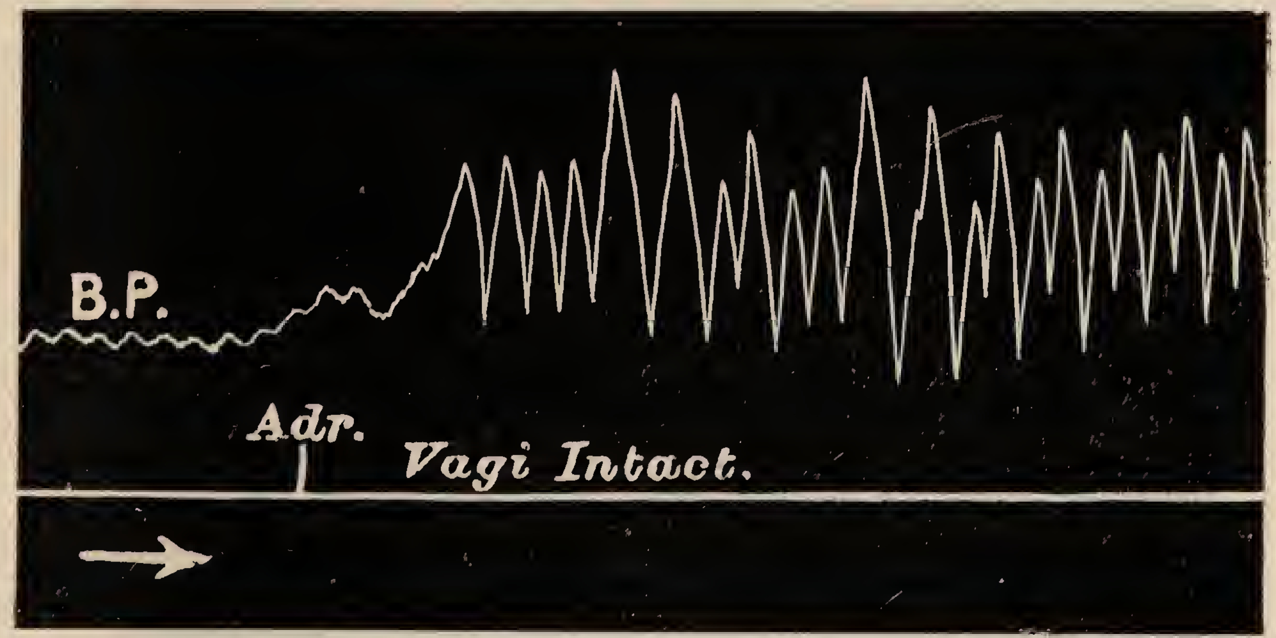


FIG. 134.—Blood-pressure tracing. Effect of injecting 0·05 mgr. adrenalin into a vein.

Note the marked slowing of the heart.

also stains with chromate, contains adrenalin. Adrenalin is completely absent from the cortex of the suprarenal glands.

When a small amount of adrenalin is injected into a blood-vessel it produces constriction of almost all the arterioles of the body, and, if the vagus nerves have been divided, an enormous rise of blood pressure is produced (fig. 133). When the vagus nerves are intact the rise of blood pressure is less (fig. 134), because, in accordance with Marey's law (p. 223), slowing of the heart takes place.

The action of adrenalin is not confined, however, to the blood-vessels, but extends to every structure in the body which is normally supplied with nerve fibres from the sympathetic system. It stimulates the nerve endings of these fibres in the structures which they supply, and the results of the injection of adrenalin are identical with those of stimulation of the entire sympathetic system. Thus it increases

the force and (if the vagi are divided) the rate of the heart, and at the same time dilates the coronary vessels, so that, in spite of the rise in blood pressure, the efficiency of the heart is maintained and its output may even become larger. It inhibits the movements of the digestive tract and (in many animals) of the bladder, but causes constriction of the ileo-colic sphincter; it may also produce sweating, erection of hairs, and dilatation of the pupil.

Adrenalin is an extremely active substance, and even 0·0025 milligram per kilo of body weight, when injected into the circulation, produces a definite rise of blood pressure.

The exact point of action of adrenalin is not on the sympathetic endings proper, but probably on some receptive substance (neuromuscular junction), which is believed to lie between the actual nerve ending and the muscular fibre which it supplies, and which is unaffected by degeneration of the nerve fibre. This can be shown by the following experiment. When the cervical sympathetic nerve, which supplies the pupil, is stimulated, or when adrenalin is injected into a vein, the pupil dilates. If the superior cervical ganglion on one side is removed, the post-ganglionic fibres degenerate, and when time has been allowed for their degeneration electrical stimulation of these fibres produces no effect on the pupil, whereas on the injection of adrenalin the pupil dilates even more fully than in the normal animal.

Adrenalin is constantly being formed by the suprarenal glands, from which it passes into the blood stream, and is thus a true internal secretion. This secretion can be increased in amount by stimulation of the splanchnic nerves, which contain secretory fibres for the suprarenal glands. The nerves may be stimulated either directly, *e.g.* by stimulation of the peripheral end of a divided splanchnic nerve, or reflexly, the centre for this reflex being either the vaso-motor centre or an adrenalin centre lying very near the vaso-motor centre. The occurrence of reflex secretion of adrenalin by the suprarenal glands can be demonstrated in the following manner: one splanchnic nerve, *e.g.* the left, is divided in the cat, so as to cut off the efferent path to one gland; and it is found that, as the result either (1) of stimulation of sensory nerves, or (2) of violent emotion, such as fear, that the adrenalin is discharged more or less completely from the right suprarenal gland, while the left gland remains unaffected. Evidently division of the splanchnic nerve, by breaking the efferent side of the reflex arc, prevents any reflex secretion of adrenalin from that gland into the blood stream. The effects of stimulation of the splanchnic nerve, and the consequent setting free of adrenalin, on the arterial blood pressure and on the constriction of arterioles outside the

splanchnic area have already been described (p. 234). Anæsthetics, such as chloroform, also excite the centre and bring about a discharge of adrenalin.

In all probability, the varying activity of the suprarenal glands, brought about by impulses reaching them along the splanchnic nerves, plays an important part in the adjustment of the vascular system to the changes constantly taking place in the body. A striking instance of this adjustment is seen, as Cannon has pointed out, in states of violent emotion, such as rage, pain, or fear. The additional adrenalin sent into the blood stream in these circumstances increases the sugar in the blood, thereby providing a further supply of sugar to the skeletal muscles, and also improves the nutrition and efficiency of the heart and the blood supply to the brain. In this way the reaction of the animal to these emotional states, by movements of attack or defence, is rendered more effective.

Owing to its action on the blood-vessels, adrenalin has proved of great value, both in checking hæmorrhage when applied locally, and in raising the arterial blood pressure in the condition of shock. In Addison's disease the repeated injection of adrenalin is stated in some cases to produce improvement, though the disease cannot be cured.

THE PITUITARY BODY (HYPOPHYSIS CEREBRI).

The pituitary body, which lies in the sella turcica and is connected by the infundibulum with the third ventricle, is a small mass consisting of two lobes, anterior and posterior. The posterior lobe originates as an outgrowth from the under surface of the brain, and at first is hollow; in man the cavity ultimately disappears and it is composed entirely of neuroglia. The anterior lobe arises as a hollow projection from the buccal epithelium, and in the adult consists of a solid mass of cells, many of which are clear and stain deeply with eosin, whereas others are very granular. Between the columns of cells are numerous capillaries.

The two lobes are separated by a narrow cleft lined by clear cells, which form the *pars intermedia* and are most abundant on the posterior wall of the cleft, partially surrounding and extending into the posterior lobe. The cells tend to become transformed into colloid material, which ultimately reaches the cavity of the third ventricle.

Complete removal of the whole gland or of the anterior lobe is followed by death in a few days, though the animals survive when minute fragments of the anterior lobe are left. After partial removal of the anterior lobe, young animals often show abnormal metabolic

changes, *e.g.* obesity, and failure of sexual development; in the adult degenerative changes take place in the sexual organs.

In man two abnormal conditions have been found in association with hypertrophy of the pituitary body. In the first place, hypertrophy has been observed in unusually tall people, and, secondly, overgrowth or tumours of the gland are found in the disease known as *acromegaly*. This occurs in adults, and is characterised by progressive enlargement of the bones of the face and extremities.

Both these changes are probably the result of increased functional activity of the anterior lobe only, since young animals to whose food the anterior lobe is added grow more rapidly than control animals which receive no such addition; extracts of the posterior lobe or pars intermedia have no influence on growth.

We may conclude, therefore, that the anterior lobe is concerned with the process of growth, hypertrophy leading to overgrowth of the skeleton, and partial removal to failure of development of the body as a whole and of the sexual glands.

Extracts of the posterior lobe, when injected into an animal, have a direct action on plain muscle all over the body; they cause constriction of the arterioles and a rise of blood pressure, contraction of the muscular coats of the digestive tract and of the bronchioles, and contraction of the uterus.

The extracts also produce an increased flow of urine, which was at first attributed to the presence of a substance having a specific effect upon the renal cells; it is probable, however, that the diuretic effect is merely an indirect result of the more rapid flow of blood through the kidney which follows the injection of the extract.

Extracts of the posterior lobe increase the secretion of milk, and after the injection a larger amount of milk is formed by the animal in the course of twenty-four hours. The active principle of the extract has not been isolated, but it is not destroyed by boiling, and is comparatively stable. It is formed entirely by the pars intermedia, extracts of the posterior lobe proper being quite inert.

The secretion of the pars intermedia is believed by some writers to pass into the cerebro-spinal fluid, but the extent to which the effects produced by extracts of the posterior lobe of the gland are normally brought about in the body is unknown.

THE THYROID AND PARATHYROID GLANDS.

The *thyroid* gland consists of two lobes, one on each side of the trachea, united by an isthmus, and is composed of closed spherical vesicles containing a viscid colloid material; the walls of the vesicles

consist of a single layer of cubical epithelial cells. The colloid material contains iodine in organic combination as a substance, *iodothyrine*, and the vesicles are bound together by connective tissue in which lie numerous blood-vessels and nerves.

The *parathyroid* glands are four in number and lie close to, or embedded in, the thyroid gland; they are quite small and consist of columns of granular cells, some of which are pigmented.

Attention was called to the importance of the thyroid gland first by the observation that the gland is atrophied in the disease known as *myxœdema*, and later by the serious and even fatal effects of its complete removal in man; this may be followed either by acute nervous symptoms accompanied by muscular spasms (tetany), or by chronic changes resembling myxœdema. The symptoms of myxœdema are obesity, dryness and thickening of the skin, falling out of the hair, slowness of mental processes and of speech; indeed, all the metabolic processes in the body become more sluggish, and the respiratory exchange is diminished.

Deficiency or absence of the gland at birth gives rise to the disease known as *cretinism*, in which growth, both mental and physical, is extremely retarded; a cretin aged fifteen to eighteen years may resemble a child of two or three years of age in its size and mental development. The symptoms, both of cretinism and of myxœdema, are due to the absence of some substance normally formed by the thyroid gland, from which it passes into the lymphatics and so into the blood stream. This is shown by the fact that extracts of the gland, or the gland itself, when given by the mouth, lead to complete recovery in myxœdema and to very marked improvement in cretinism.

The action of the gland seems to depend partly or wholly upon the presence of iodothyrine, since the activity of the extracts is greater when they contain much iodine. It is evident that the thyroid gland exerts an important influence on the metabolism of the body, including the nervous system. This is further shown by the observation that in myxœdema much larger quantities of sugar can be taken by the mouth without producing alimentary glycosuria than is the case in normal persons.

The effects of removal of the gland in animals are of two kinds. Frequently, especially in carnivora, its removal is rapidly followed by acute symptoms, of which the most striking are spasms of the skeletal muscles known as tetany, and in young animals death may occur in a few days. The acute stage may be followed or may be replaced by chronic disturbance of nutrition, and in monkeys typical myxœdema similar to that seen in man has been observed. Opinion is divided as

to the part played by the absence of thyroid and parathyroid tissues respectively in the production of the symptoms which follow the removal of the entire gland. Some consider that parathyroid tissue has no distinct function of its own, but is merely undeveloped thyroid tissue. They find that when the greater part of the thyroid is removed the parathyroids increase in size and contain colloid material; and they regard all the symptoms which follow the removal of the thyroid and parathyroid glands as the result of the removal of thyroid tissue proper.

Others believe that removal of the parathyroid glands produces the acute nervous symptoms, and more especially tetany, whereas removal of the thyroid gland alone brings about chronic changes in metabolism and nutrition. The difficulty of determining the function of the parathyroid tissue is due to the fact that in many animals it is deeply embedded in the substance of the thyroid gland. When this is the case, it is difficult either to remove the thyroid gland without also damaging the parathyroid tissue, or to remove the parathyroid glands without serious injury to the thyroid glands.

The balance of evidence, however, favours the view that the functions of the thyroid and parathyroid tissue are distinct, and that the former is concerned solely with metabolism, tetany being the result of removal of the parathyroids.

THE SPLEEN.

The spleen is a solid organ enclosed in a capsule, which is partly fibrous and partly consists of plain muscular tissue. The capsule sends trabeculæ, also containing unstriated muscle, into the interior of the organ; these branch to form a framework, in the interstices of which lies the spleen pulp. This consists of a fine network of connective-tissue fibrils, covered by endothelial cells, and containing in its meshes lymphocytes, red blood corpuscles, and large cells which are amœboid and often contain partly broken-down red corpuscles. Multinucleated giant cells are also sometimes present.

The outer coat of the arteries in the spleen consists of lymphoid tissue, an enlargement of which is present on each arteriole and forms a Malpighian corpuscle. Some capillaries are found in the Malpighian bodies, but, with this exception, the arterioles open directly into the spleen pulp, from which the blood is again gathered up to leave the spleen along the splenic vein. The blood thus comes into direct contact with the tissue elements of the spleen, whereas in almost every other organ of the body it is separated from the tissues by a capillary wall.

The flow of blood through the spleen is assisted by the alternate

contraction and relaxation of the muscular tissue in its capsule and trabeculæ; this rhythmic contraction, which takes place about once a minute, can be recorded by enclosing the spleen in a plethysmograph connected with a tambour. The muscular fibres are supplied with nerves from the sympathetic system, and the direct or reflex stimulation of these nerves, or the injection of adrenalin, produces contraction of the muscle and diminution of the volume of the spleen.

The functions of the spleen are not fully known, though it is not essential to life and can be removed without serious after-effects. The presence of partially disintegrated red blood corpuscles in the phagocytic cells of the pulp indicates that it is concerned in the destruction of red cells, but the extent to which this takes place is not known. The spleen normally contains a relatively large amount of iron, and when the destruction of red cells in the body is excessive this amount is increased. Further, the Malpighian bodies undoubtedly form lymphocytes. In all probability the spleen also takes part in the production of uric acid, since it contains enzymes which can convert xanthine and hypoxanthine into uric acid.

In many infective diseases the spleen is enlarged, and it seems to play a part in the protection of the body against disease by removing micro-organisms from the blood, possibly also by destroying the poisons formed by such organisms.

THE THYMUS.

The thymus is composed of lobules united by connective tissue; each lobule consists of an outer, denser cortex and an inner medullary part, the cortex being subdivided by strands of connective tissue into a number of compartments. Both the cortex and medulla are composed of a network of fibrils covered with endothelial cells, the meshes being occupied by lymphocytes. In the medulla are found a number of small masses of flattened epithelial cells arranged concentrically; they are called Hassall's corpuscles, and represent the remains of part of the epithelium of the third visceral pouch. The gland is abundantly supplied with blood-vessels. In man it reaches its maximum size during the first two or three years of life, and then becomes smaller, being almost completely absent in the adult. After its removal in animals, the testes develop more rapidly, and conversely castration delays the atrophy of the thymus. When young animals receive fresh thymus with their food sexual maturity is delayed, and, in the male, degeneration of the testis takes place.

CHAPTER XVI.

REPRODUCTION.

In all except the lowest forms of life, the continuance of the species is effected by means of certain tissues set apart for this purpose. These form cells which develop into a new animal of the same species, the process constituting reproduction. In most animals these cells are of two kinds, namely, spermatozoa and ova, formed by the reproductive organs of the male and female respectively; a spermatozoon and ovum fuse to form a new cell which develops into an animal resembling its parents in its general characters. This, again, is capable of reproducing itself, and the cycle of life is completed.

THE MALE REPRODUCTIVE ORGANS.

These consist of the testes, which form spermatozoa, and of accessory organs, namely the vesiculæ seminales, the prostate gland, the glands of Cowper, and the penis. Each testis is covered by a strong fibrous capsule, the *tunica albuginea*, from which trabeculæ pass into the gland, dividing it into lobules which contain the seminal tubules. Each tubule is convoluted, and consists of a lining epithelium several layers thick, resting upon a laminated basement membrane. The cells nearest the basement membrane are called *spermatogonia*; these divide, giving rise to the *spermatocytes*, which lie more internally. Within the layer of spermatocytes, and formed from them by division, are the *spermatids*, which develop into spermatozoa. Lying in the connective tissue between the tubules are groups of polyhedral cells, called interstitial cells. The seminal tubules lead into straight tubules (*rete testis*) which open into the epididymis; this is a convoluted tube lined by ciliated cells, and is continued as the *vas deferens*, a thick muscular tube which opens into the prostatic part of the urethra. The vesiculæ seminales are branched sacculated outgrowths from the vas deferens. The prostate gland surrounds the first part of the

urethra, and is made up of numerous branched, glandular tubes supported by connective tissue and unstriated muscular tissue.

The penis consists of erectile tissue, which forms the corpus spongiosum and the two corpora cavernosa, and it contains the urethra; the erectile tissue is made up of a meshwork of elastic and muscular tissue into which arterioles open directly, the blood escaping into veins. When the muscle fibres are relaxed the spaces become distended with blood, causing erection of the organ.

The formation of spermatozoa begins at puberty, and each spermatozoon consists of a head, body, and tail, and is actively motile. The fully formed spermatozoa pass from the testis into the epididymis and vas deferens, and so to the seminal vesicles.

FEMALE REPRODUCTIVE ORGANS.

The female generative organs are the ovary, Fallopian (uterine) tubes, uterus, and vagina.

The **Ovary** is a solid organ composed of fibrous tissue (stroma), with many spindle-shaped cells, and is covered by a layer of cubical cells called the germinal epithelium. Groups of interstitial cells are found in the stroma, similar to those which occur in the testis. The ovary contains many vesicles of varying size (Graafian follicles), and a large number of primordial follicles; the latter are formed during fœtal life from down-growths of the germinal epithelium into the stroma, and each consists of an ovum surrounded by a layer of flattened cells.

The *ovum* is a large spherical cell enclosed in a striated envelope called the zona pellucida (striata); its protoplasm, which is abundant, is filled with fatty and albuminous granules, and contains a spherical nucleus (germinal vesicle) and nucleolus.

At puberty some of the primordial follicles develop into Graafian follicles (vesicular ovarian follicles). The epithelial cells covering the ovum multiply to form a mass in which fluid appears, separating the epithelium into two parts, an outer layer, the *membrana granulosa*, forming the wall of the follicle, and an inner layer, the *discus proligerus*, surrounding the ovum. At this stage the whole follicle is enclosed in a fibrous capsule derived from the stroma. As the amount of fluid increases, the follicle approaches the surface of the ovary, and eventually bursts, the ovum being set free and passing into the Fallopian tube. The process just described is called *ovulation*. The space left by the escape of the ovum and fluid is filled up by the ingrowth of vascular processes from the surrounding tissue, forming the *corpus luteum*, so called because its cells are yellowish in colour owing to the presence of

a fatty pigment, *lutein*. It gradually undergoes fibrous changes and disappears within two months. If pregnancy occurs, the corpus luteum becomes much larger and does not disappear until after parturition. The primordial ova are extremely numerous in the ovary, but only a small proportion of them develop into Graafian follicles, and only a few of the latter reach maturity and burst, the others, after developing to a certain extent, undergoing atrophy. During sexual life ovulation usually occurs once a month, a single ovum being discharged on each occasion. The process is intimately bound up with menstruation.

The Uterus.—The uterus consists of two parts, the body and the cervix. Its cavity is lined by a thick mucous membrane, composed of soft connective tissue covered by ciliated epithelium which dips down into the membrane to form long tubular glands.

The mucous membrane rests on a thick muscular coat arranged in two layers. The fibres of the outer layer run chiefly longitudinally, but some run circularly; the fibres of the inner layer, which is much thicker than the outer one, run circularly, and are really a greatly hypertrophied muscularis mucosæ.

The Fallopian (uterine) tube consists of a mucous membrane thrown into numerous longitudinal folds and lined by ciliated epithelium. The mucous membrane rests upon a muscular coat, the outer fibres being longitudinal and the inner circular.

Both the uterus and Fallopian tubes are covered by a serous membrane derived from the peritoneum.

Menstruation.—This marks the onset of puberty, and occurs first between the ages of 13 and 16; as a rule, it recurs once a month until about the age of 45, its cessation at this age being called the *menopause*.

Each month the mucous membrane of the uterus becomes congested and thickened, and eventually some of the blood-vessels of the membrane rupture; the escaping blood, together with the superficial epithelium of the uterus and the secretion of the uterine glands, form the menstrual flow, which lasts four or five days, the loss of blood varying from 100 to 300 c.c. When it ceases, the mucous membrane of the uterus is gradually regenerated, and returns to its original condition.

Menstruation is associated with feelings of malaise and often with a slight rise of temperature. It is absent during pregnancy, and usually during lactation, and is undoubtedly related to and dependent upon ovulation, though the latter may either precede or follow the menstrual flow. Menstruation ceases after the removal of the ovaries, and also at the menopause, when ovulation no longer takes place; its object appears to be to render the condition of the uterus, at the end of the

menstrual period, suitable for the reception and development of the ovum if fertilisation takes place. In many of the lower animals a somewhat similar change in the uterus, known as the *œstrus*, occurs at certain seasons of the year, and is accompanied by ovulation and sexual activity.

Maturation of the Ovum.—After being discharged from the ovary the ovum undergoes certain changes known as maturation. When a cell divides in other (somatic) tissues the process is initiated by changes in the nucleus and is known as mitosis. The network of chromatin in the nucleus breaks up into a number of segments called chromosomes, each composed of rows of granules; the number of chromosomes thus formed is constant for every somatic cell for a given species of animal, and in man the number is sixteen. The next stage consists in the splitting of each chromosome longitudinally into two halves, which travel to opposite ends of the cell. While this is taking place the cell protoplasm constricts and then divides between the nuclei to form two cells, each of which contains the same number of chromosomes as the original cell. Finally, the chromosomes of each daughter cell fuse into a single chromatin filament.

In the germ cells a different form of cell division takes place, and is known as *heterotype* mitosis. The ovum divides twice. The daughter cells from the first division differ greatly in size, and the smaller one, called the first *polar body*, breaks up and disappears. The characteristic feature of this division is that the number of chromosomes formed is only half that occurring in a somatic cell in the same animal. The larger cell, which contains only half the normal number of chromosomes, divides again to form two daughter cells, one of which is small, the second polar body, whereas the other is large and constitutes the mature ovum.

A similar process takes place in the formation of spermatozoa, except that the four daughter cells, spermatids, formed from the spermatocytes, all develop into spermatozoa; and in man each spermatozoon and mature ovum contains eight chromosomes, whereas the somatic cells contain sixteen.

Fertilisation takes place as a result of the introduction of spermatozoa into the vagina during the act of coitus. The motile spermatozoa travel into the uterus and Fallopian tubes, where they may live for some days. If a spermatozoon penetrates into an ovum, it loses its tail, changes take place in its head and neck, and it is converted into a male pronucleus, which fuses with the nucleus of the ovum (female pronucleus) to form a new cell containing the normal number of chromosomes; this process constitutes fertilisation.

The cell thus formed at once divides, and when the ovum which has been fertilised in the Fallopian tube reaches the uterus, it has already divided and subdivided to form a small mass of cells called a *morula.*

The further development of the morula takes place in the uterus and constitutes pregnancy. The morula makes its way into the uterine mucous membrane, which then consists of three parts : namely, (1) the *decidua basalis,* lying between the embryo and the muscular wall of the uterus ; (2) the *decidua capsularis* (*reflexa*), between the embryo and the cavity of the uterus ; and (3) the *decidua vera,* lining the remainder of the uterus. As the embryo grows, it becomes enclosed in a sac filled with fluid and called the amnion ; surrounding the amnion is a vascular membrane, the chorion, from which blood-vessels pass to and from the fœtus in the umbilical cord. After the third month of pregnancy the fœtus receives its nutrition from the *placenta,* which is formed partly from maternal and partly from fœtal tissue. It consists essentially of large blood spaces in the *decidua basalis,* into which open the uterine arteries, and from which the blood of the mother is carried into the uterine veins. Projections from the chorion (chorionic villi) containing fœtal blood-vessels lie in these spaces and are bathed by the maternal blood ; the blood reaches the villi along the umbilical arteries, and is returned to the fœtus in the umbilical vein. The maternal and fœtal blood are thus separated by a double layer of epithelium, and the nutrition of the fœtus is effected by the diffusion of oxygen and nutritive material through this epithelium.

Parturition.—The average duration of pregnancy is 280 days, during which the muscular wall of the uterus not only increases in size, but becomes greatly thickened. Parturition is brought about by rhythmic contraction of the uterine muscle, and the fœtal membranes and their contained fluid are forced through the os uteri, which becomes fully distended. This, the first stage of labour, ends when the os uteri is fully dilated ; and the membranes rupture about this time.

The fœtal head then enters the pelvis, and the uterine contractions become more prolonged and frequent, being accompanied by voluntary contractions of the abdominal muscles. The fœtus is gradually forced through the pelvic canal and vulva, the head normally being born first. The second stage of labour ends when the child is born. The whole process of parturition varies greatly in duration, and may last twenty-four hours. Shortly after the birth of the child the uterus contracts further and expels the placenta.

After parturition the uterus rapidly decreases in size, this being known as *involution.*

The Mammary Gland.—The mammary gland consists of a number

of lobules embedded in fat and areolar tissue. Each lobule is composed of alveoli lined by columnar epithelium, resting on a basement membrane. The ducts open on to the nipple, and are lined by cubical epithelium; their walls are said to contain unstriated muscular fibres. During the secretion of milk the superficial part of the cells, which contains fat globules and secretory granules, disintegrates and is cast off to form part of the secretion; during the periods of rest the cell substance is re-formed.

The development of the mammary gland during pregnancy is brought about by the influence of hormones derived from the reproductive organs. In the earliest stage of pregnancy a hormone appears to be formed in the corpus luteum, and if a Graafian follicle is artificially ruptured in an animal the mammary glands develop for a short time apart from pregnancy. Later, another hormone is possibly formed by the fœtus itself, since it has been shown that injection of an extract of fœtal tissue into a virgin rabbit leads to growth of the mammary glands. That their development is due to chemical and not to nervous influence is further indicated by the fact that, even after the severance of all nerves to the mammary gland, it undergoes normal development during pregnancy.

The Secretion of Milk.—Very little is known as to the mechanism by which the secretion of milk is brought about, although it can undoubtedly be influenced through the nervous system. As already mentioned, the injection of extracts of the hypophysis increases the secretion of milk, but it is not known whether the hypophysis normally plays any part in the process.

SUBSIDIARY FUNCTIONS OF THE REPRODUCTIVE ORGANS.

The reproductive glands not only form the essential reproductive elements, namely, spermatozoa and ova, but influence very markedly the growth and development of the rest of the organism.

In the male the onset of puberty, *i.e.* the formation of spermatozoa in the testis, is associated with the development of secondary sexual characteristics, such as changes in the larynx, deepening of the voice, and the growth of hair on the face and pubes. If the testes are removed before puberty these characters do not develop, and the body remains infantile. After puberty castration leads to atrophy of the accessory genital organs. In the lower animals castration also prevents the appearance of secondary sexual characteristics, such as the antlers of the stag, or the comb of the cock.

In the female extirpation of the ovaries prevents the occurrence

of menstruation and the development of the mammary gland, which normally take place at puberty; their removal after puberty brings about the cessation of menstruation.

The normal changes accompanying sexual development appear to depend for their occurrence upon an internal secretion formed by the testes or ovaries, and they furnish a striking illustration of the chemical interrelation between the different parts of the body. The hormones concerned in the growth of secondary sexual characteristics have not been isolated, and the exact site of their formation is doubtful; some observers believe that they are formed by the interstitial cells of the testis and ovary, since ligature of the vas deferens, while causing atrophy of the seminiferous tubules, does not affect the interstitial cells or the development of secondary sexual characteristics.

HEREDITY.

When reproduction takes place the offspring bear a general resemblance to the parents, though differing in detail from both of them. The transmission of the qualities of the parent is carried out solely by the germ plasm, and the hereditary qualities are present in the nuclei of the spermatozoon and ovum respectively. The spermatozoon, however, appears to have a double function; in addition to containing potentially the characters of the male parent, it acts as a chemical or physical stimulus to segmentation and division of the ovum. This latter function can, to some extent, be replaced in certain invertebrates (*e.g.* sea urchins) by producing physical changes in the environment of the ovum; and under such conditions unfertilised ova have been made to develop partially or completely into normal larvæ.

The formation of polar bodies, and the analogous process taking place in the formation of spermatids prior to fertilisation, involves the loss of part of the nuclear substance, and therefore, probably, of part of the parental qualities transmitted to the offspring. On this account the characters of the offspring show variations from those of the parents. In many cases these variations have proved advantageous in the struggle for existence by adapting the animal more closely to its environment; and the survival of those most fitted for their surroundings has led to the evolution of the higher forms of life.

An important problem in heredity is whether the characters of the offspring represent a mean between those of the parents, or whether a parental character can be transmitted completely or not at all. There is evidence that in many cases the latter is true, and the conditions under which this transmission occurs are known as *Mendel's law*. When tall

and dwarf peas, for example, are crossed, all the seeds produce tall plants. If the seeds from these tall plants are crossed with each other, three-quarters become tall and one-quarter are short. In this case the qualities of tallness and shortness have not fused, and the quality of tallness is either present or absent. When it is present the plant is tall, even though the quality of shortness is also present; tallness is said, therefore, to be a *dominant*, and shortness a *recessive* character. If the recessive character alone is present the plant is short.

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PRINTED BY NEILL AND CO., LTD., EDINBURGH.